RADEMIKIBART

CBP-201-207

A Phase 2, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Rademikibart as an Add-on Treatment for Acute Exacerbation in Participants With Chronic Obstructive Pulmonary Disease and Type 2 Inflammation

Investigational Product:	Rademikibart (CBP-201)
Protocol Number:	CBP-201-207
IND #:	154808
Development Phase:	2
Sponsor:	Connect Biopharm LLC (dba, Connect Biopharma) 3580 Carmel Mountain Road, Suite 200 San Diego, CA 92130 USA
Version and Date:	1.2, 09 June 2025

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SIGNATURE PAGE

PROTOCOL TITLE: A Phase 2, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Rademikibart as an Add-on Treatment for Acute Exacerbation in Participants with Chronic Obstructive Pulmonary Disease and Type 2 Inflammation

PROTOCOL NUMBER: CBP-201-207

PROTOCOL VERSION: 1.2 (dated 09 June 2025)

The protocol has been approved by Connect Biopharma.

Sponsor's Authorized Officer:

Signed by:
Kimberly Manhard
Signer Name: Kimberly Manhard
Signing Reason: I approve this document
Signing Time: 6/9/2025 | 7:09:45 PM PDT
9A274C00844A4DD39990CF408669E960

Kimberly J Manhard
Chief Development Officer

INVESTIGATOR'S AGREEMENT

PROTOCOL TITLE: A Phase 2, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Rademikibart as an Add-on Treatment for Acute Exacerbation in Participants with Chronic Obstructive Pulmonary Disease and Type 2 Inflammation

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1. All documentation for this trial that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this trial protocol, Investigator's Brochure(s) (IB), Case Report Forms (CRFs), and scientific data not in the public domain.
2. The trial will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the trial protocol without the prior written approval of the Sponsor and the IRB/IEC, except where necessary to avert an immediate hazard to the participants.
3. I have read the protocol, and I agree that (a) I am qualified by education, experience, and training to conduct this trial and (b) the trial will be conducted in compliance with the protocol and in accordance with the principles of the current version of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), and with all other government, local and regional regulations.
4. I acknowledge that I am responsible for the overall trial conduct. I agree to personally conduct or supervise the described clinical trial. I agree to ensure that all associates, colleagues and employees assisting in the conduct of the trial at my site are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the trial. I will provide copies of the protocol, IB, and all other information on the investigational product that were furnished to me by the Sponsor to all physicians and other trial personnel responsible to me who participate in this trial and will discuss this material with them to ensure that they are fully informed regarding the investigational product and the conduct of the trial.
5. I agree to keep records on all participant information (eg, medical records, Case Report Forms, and informed consent statements), investigational product shipment and return forms, and all other information collected during the trial in accordance with local and national Good Clinical Practice guidelines.

Reviewed by:

Printed Name of Investigator and Research Center

Signature of Investigator Date

1. SYNOPSIS

Sponsor:	Connect Biopharma 3580 Carmel Mountain Road, Suite 200 San Diego, CA 92130 USA
Protocol Number:	CBP-201-207
Trial Title:	A Phase 2, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Rademikibart as an Add-on Treatment for Acute Exacerbation in Participants with Chronic Obstructive Pulmonary Disease and Type 2 Inflammation
Short Title:	Rademikibart Add-on Treatment of an Acute COPD Exacerbation (Seabreeze STAT COPD)
Trial Phase:	2
Interventional Treatment:	Rademikibart (CBP-201) is a recombinant monoclonal antibody that binds human interleukin (IL)-4 receptor alpha (Rα), a common subunit of the IL-4 and IL-13 receptor dimers. Rademikibart blocks signaling from both IL-4 and IL-13, which are thought to play a role in the pathogenesis of type 2 inflammatory airway diseases, including in a subgroup of participants with chronic obstructive pulmonary disease (COPD).
Planned Number of Trial Sites(s):	Approximately 50 sites.
Planned Participant Enrollment:	Approximately 160 participants will be randomized which may be adjusted following the planned interim analysis (IA) due to a sample size re-estimation.
Population:	Adult participants (40 to 80 years, inclusive) with COPD characterized by an eosinophilic phenotype who require an urgent healthcare visit for treatment of an acute exacerbation. This trial will screen participants through 2 different channels: 1. Participants who consent to participate in the trial while in a stable condition, and 2. Participants who consent to participate in the trial at an urgent healthcare visit for acute COPD exacerbation.
Trial Duration:	**For participants who consent to participate in the trial while in a stable condition**, the trial duration will be up to 34 weeks. This includes a Screening Period of up to 26 weeks, a 28-day Treatment Assessment Period, and a 28-day Follow-up Period. **For participants who consent to participate in the trial during an urgent healthcare visit for an acute COPD exacerbation**, the trial duration will be approximately 8 weeks. This includes a Screening Period

	of up to 48 hours, a 28-day Treatment Assessment Period, and a 28-day Follow-up Period.
Trial Design; Interventional Treatment Dosing Schedules:	This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, interventional trial in participants with an acute COPD exacerbation with type 2 inflammation in the urgent healthcare setting to compare rademikibart plus standard therapy to standard therapy (plus placebo). For the purposes of this trial, an urgent healthcare setting may include an emergency department (ED), a hospital inpatient ward, or an urgent healthcare facility equipped to provide the level of care specified in this protocol. The trial is designed to evaluate the efficacy and safety of a single 600 mg subcutaneous (SC) dose (administered as 4 separate 150 mg injections) of rademikibart as adjunct therapy to standard therapy in adult participants with COPD characterized by an eosinophilic phenotype (peripheral blood eosinophil count of ≥300 cells/µL at Screening Visit 1b or as part of the assessment of the index acute COPD exacerbation within 72 hours prior to Screening) who require urgent healthcare treatment for an acute COPD exacerbation. Approximately 160 adult participants will be randomized in a 1:1 ratio to 1 of the following double-blinded treatment groups, stratified by severity of the acute COPD exacerbation (requiring hospitalization or not [yes/no]) at baseline, and baseline smoking status [current or former]): • **Rademikibart** 600 mg dose administered as 4 SC injections of 1 mL (150 mg) each. • **Matching Placebo** administered as 4 SC injections of 1 mL each. Investigational product (IP; rademikibart 600 mg SC or placebo SC) will be administered on Day 0. One IA is planned when approximately 80 participants have completed the Week 4 Visit, and the final analysis for the trial will be conducted after all participants have completed Week 8 or the End of Trial (EOT) Visit.

Trial Objectives and Endpoints:

Primary Objective	Primary Endpoint
• To evaluate the efficacy of rademikibart compared to placebo as an adjunct to standard therapy on the treatment failure rate within 28 days after randomization in participants with COPD and an eosinophilic phenotype experiencing an acute COPD exacerbation.	• Treatment failure rate within 28 days after randomization.
Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of rademikibart compared to placebo as an adjunct to standard therapy on subsequent COPD exacerbations in participants with COPD and an eosinophilic phenotype experiencing an acute COPD exacerbation.	• Rate of new moderate and severe COPD exacerbations over the 28 days after randomization. • Time to the first new moderate or severe COPD exacerbation in the 28 days after randomization. • Mean CFB in clinical respiratory symptoms of COPD using the E-RS: COPD comprised in the EXACT-PRO through Week 1, Week 2, and Week 4. • Absolute CFB in post-BD FEV1 at Day 3, Week 1, and Week 4.
• To evaluate the safety of rademikibart compared to placebo when administered as an adjunct to standard therapy in participants with COPD and an eosinophilic phenotype experiencing an acute COPD exacerbation.	• Incidence of AEs, including SAEs, AESIs, and DILI reported. • Incidence of UADEs. • Incidence of injection site reactions. • Changes in safety laboratory parameters.

	• Changes in vital signs, physical examinations, and ECG parameters. AE = adverse event; AESI = adverse event of special interest; BD = bronchodilator; CFB = change-from-baseline; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; E-RS: COPD = Evaluating Respiratory Symptoms in COPD; DILI = drug-induced liver injury; EXACT-PRO = Exacerbations of Chronic Obstructive Pulmonary Disease-Tool – Patient-Reported Outcome; FEV_1 = forced expiratory volume in 1 second; SAE = serious adverse event; UADE = unanticipated adverse devise effect.
Eligibility Criteria:	**Inclusion Criteria** Participants are eligible to be included in the trial only if ALL of the following criteria apply: 1. Written informed consent obtained prior to performing any protocol-related procedures. 2. Adults (40 to 80 years, inclusive) at the time of signing the informed consent. 3. Body weight of ≥45 kg and body mass index within the range 16 to 35 kg/m^2 (inclusive) at Screening. 4. Physician-diagnosed COPD with duration of ≥12 months by medical chart or participant report; COPD is defined as dyspnea and/or chronic productive cough with current or historic evidence of spirometry confirming airflow obstruction (post-BD FEV_1/forced vital capacity [FVC] ≤70%). 5. Must have experienced at least 1 COPD exacerbation requiring the use of systemic corticosteroids (oral or parenteral) within the previous 12 months prior to Screening. 6. Participants who consent to participate in the trial while in a stable condition must have a documented historical peripheral blood eosinophil count of ≥250 cells per microliter (μL) within 12 months prior to Screening Visit 1a. 7. Current or former smokers with a smoking history of ≥10 pack-years. *Note: This includes tobacco, marijuana, and vaping products.* 8. In the opinion of the Investigator, participant is willing and able to comply with all trial visits and trial-related procedures (such as willing and able to perform entries of daily electronic diary (e-diary) patient-reported outcomes [PRO]s). 9. Women of childbearing potential, unless surgically sterile (including tubal ligation) and/or at least 2 years postmenopausal, should have a

	confirmed negative serum beta-human chorionic gonadotropin (β-hCG) test at Screening Visits 1a and/or 1b and agree to use a highly effective method of avoiding pregnancy from trial recruitment through Day 56. *Note: A female is considered of childbearing potential following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.* **Additional Inclusion Criteria for Current Acute COPD Exacerbation** 10. Current acute COPD exacerbation requiring an urgent healthcare visit for treatment. *Note: COPD acute exacerbation is defined as an acute increase in symptoms (1 or more of the following: cough frequency and severity, sputum production, dyspnea) beyond normal day-to-day variations leading to a change in medication.* *For the purposes of this trial, an urgent healthcare setting may include an ED, a hospital inpatient ward, or an urgent healthcare facility equipped to provide the level of care specified in this protocol. The primary reason for ED visit, urgent healthcare visit, or hospitalization is for acute COPD exacerbation.* 11. Peripheral blood eosinophil count of ≥300 cells/μL at Screening Visit 1b or as part of the assessment of the index acute COPD exacerbation within 72 hours prior to Screening Visit 1b. 12. Requires systemic corticosteroids as standard of care (SoC) treatment in the urgent healthcare setting for the current acute COPD exacerbation. **<u>Exclusion Criteria</u>** A participant who meets any of the following criteria will be ineligible to participate in this trial: 1. Previously received rademikibart; or a known systemic hypersensitivity or anaphylaxis to any biologic therapy, including any excipients. 2. Regular use of immunosuppressive medication (including but not limited to maintenance daily prednisolone, hydrocortisone, azathioprine, or weekly methotrexate) 12 weeks or 5 half-lives prior to randomization, whichever is longer. 3. Scheduled elective surgery or other procedures requiring general anesthesia during the trial.

	4. Current diagnosis or a history of asthma, according to the Global Initiative for Asthma; or participants with a current diagnosis or history of Asthma COPD Overlap Syndrome. 5. Other respiratory disorders: A diagnosis of alpha-1 antitrypsin deficiency as the underlying cause of COPD, lung cancer, clinically overt bronchiectasis (*Note: focal fibrotic pulmonary lesions are not exclusionary*), primary pulmonary hypertension, interstitial lung diseases, or any other respiratory condition that might, in the opinion of the Investigator, compromise the safety of the participant or affect the interpretation of the results. 6. Unstable ischemic heart disease, cardiomyopathy, heart failure (New York Heart Association Class III or IV), uncontrolled hypertension which, in the Investigator's judgement, may put the participant at risk or negatively affect the outcome of the trial. Cardiac arrhythmias including paroxysmal (eg, intermittent) atrial fibrillation are excluded. Participants with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (ie, selective beta blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) and stable appropriate level of anticoagulation for at least 6 months may be considered for inclusion. 7. Transient ischemic attack or stroke <6 months from Screening Visit; hospitalization for any cardiovascular or cerebrovascular event <6 months from Screening Visit. *Note: this criterion should be confirmed at both Screening Visit 1a and Visit 1b.* 8. Participants with a history of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, ophthalmologic, respiratory, gastrointestinal, cerebrovascular, substance and/or alcohol abuse, or other significant medical illness or disorder which, in the Investigator's judgement, could interfere with the trial or require treatment that might interfere with the trial. Specific examples include but are not limited to poorly controlled diabetes. 9. Another clinically significant pulmonary or systemic disease associated with an elevated peripheral blood eosinophil count (eg, allergic bronchopulmonary aspergillosis, eosinophilic granulomatosis with polyangiitis, hyper-eosinophilic syndrome, and helminth infection). 10. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis), despite

	infection resolution; or unusually frequent, recurrent or prolonged infections, in the opinion of the Investigator. 11. History of known immunodeficiency disorder (including human immunodeficiency virus [HIV]-1 or HIV-2). 12. Known medical history of hepatitis B or C. 13. History of alcohol abuse and/or drug abuse within 12 months prior to Screening Visit 1a and/or 1b. 14. History of cancer except basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy >1 year prior to entry or other malignancies treated with apparent success with curative therapy >5 years prior to entry. 15. Having undergone lung volume reduction surgery or lung resection for any other reason, eg, lung carcinoma. 16. Chronic treatment with long-term oxygen therapy (LTOT) or nocturnal oxygen therapy required for >15 hours a day. Oxygen pro re nata (PRN) use (ie, ≤15 hours per day) is not exclusionary. Oxygen use during an exacerbation is permitted. 17. Participants on long-term macrolide (eg, azithromycin) therapy, unless on stable therapy for >12 months, with the exception of prior treatment for an acute COPD exacerbation. **Additional Exclusion Criteria for Current Acute COPD Exacerbation** 18. Fever recorded as >38°C measured using the tympanic temperature and/or a suspected pulmonary infection (chest radiograph demonstrating consolidation). 19. Any condition (ie, respiratory failure necessitating non-invasive or invasive ventilation, or impending hemodynamic compromise, or impending intensive care unit [ICU] admission) that, in the opinion of the Investigator, would interfere with evaluation of the IP or interpretation of trial results. 20. Current acute COPD exacerbation for which SoC was started >48 hours prior to Screening Visit 1b. 21. Chest X-ray or computed tomography (CT) scan at Screening Visit 1b reveals evidence of clinically significant abnormalities not believed to be due to the presence of COPD, or a clinically significant pulmonary infection (chest radiograph demonstrating consolidation) identified by chest X-ray (CT scan) at Screening Visit 1b. 22. Participants with a prolonged QTc interval (male >450 msec, female >470 msec, Fridericia correction); any other clinically significant

	abnormalities in electrocardiogram (ECG) at Screening, in the opinion of the Investigator. 23. An alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥2.5 × the upper limit of normal (ULN) and/or bilirubin level ≥1.5 × ULN at Screening Visit 1b 24. Any other acute illness other than the acute COPD exacerbation at the start of the trial at Visit 1b. 25. Any clinically significant abnormal findings in physical examination, vital signs, hematology, clinical chemistry or urinalysis which, in the opinion of the Investigator, may put the participant at risk because of their participation, or may influence the results of the trial or their ability to complete the duration of the trial. 26. Female participant who is pregnant, lactating or breast-feeding, or has a positive urinary beta-human chorionic gonadotropic (β-hCG) test. 27. Evidence of clinically significant non-respiratory active infection, including ongoing chronic infection. 28. Receipt of any marketed nonbiologic drug that modulates type 2 cytokines (eg, suplatast tosilate) 30 days or 5 half-lives prior to randomization, whichever is longer. 29. Receipt of any marketed (eg, dupilumab or other monoclonal antibody) or any investigational biologic for COPD or other diseases within 16 weeks or 5 half-lives prior to randomization, whichever is longer. 30. Live, attenuated vaccinations within 4 weeks prior to randomization or planned live, attenuated vaccinations during the trial. 31. Treatment with oral corticosteroids and/or hospitalization for an exacerbation of COPD (not for the index acute COPD exacerbation) completed less than 4 weeks prior to randomization. 32. Donation of blood, plasma or platelets within 90 days prior to randomization. 33. Receipt of intravenous immunoglobulin or blood products within 30 days before randomization into the trial. 34. Receipt of any investigational nonbiologic drug within 30 days or 5 half-lives prior to randomization, whichever is longer.
IPs and Route of Administration:	Rademikibart drug product is provided as a colorless-to-pale yellow sterile solution at 150 mg/mL concentration in a 1 mL single-use pre-filled (PFS) syringe that delivers 1.0 mL solution.

	Placebo for rademikibart is provided as colorless-to-pale yellow sterile solution containing the same excipients as the rademikibart drug product in a 1 mL single-use PFS that delivers 1.0 mL solution. The IPs will be administered by SC injection.
Trial Evaluation	
Efficacy:	Efficacy will be assessed via evaluations of the treatment failure rate, subsequent acute COPD exacerbations, spirometry assessments, venous blood gas (VBG) analysis (only for the hospitalized participants), PROs, and healthcare resource utilization and economics per the Schedule of Assessments. PRO assessments carried out at trial visits will be completed as the first assessment in the visit schedule before spirometry or any other trial procedure. **Treatment Failure:** Treatment failure is defined as death due to any cause, (re)admission to a hospital for COPD, ED (re)visit or unscheduled medical visit for worsening of COPD symptoms, or the necessity to intensify pharmacologic treatment (including second course of systemic steroids for COPD exacerbation) within 28 days after randomization. **Acute COPD Exacerbation Assessments and Severity of Exacerbations as Defined by Protocol:** COPD exacerbation assessment will be performed throughout the 8-week post-treatment Follow-up Period at trial visits and using the e-diary data. Exacerbations of COPD are defined as clinically significant worsening of COPD symptoms, including increases in dyspnea, wheezing, cough, sputum volume, and/or increase in sputum purulence. Exacerbation severity was further defined as moderate if treatment with systemic corticosteroids and/or antibiotics was required, or severe if they resulted in hospitalization or observation for over 24 hours in an ED or urgent healthcare facility. All other exacerbations will be classified as "mild." For both moderate and severe events to be counted as separate events, they must be separated by at least 14 days. **Spirometry:** • Pre-BD measured parameters, including FEV_1 and FVC. • Post-BD measured parameters, including FEV_1 and FVC. **VBG Analysis (for Hospitalized Participants Only):** • VBG, including pH, partial pressure of oxygen, partial pressure of carbon dioxide, oxygen saturation, and the bicarbonate (HCO_3^-) concentration will be measured. **PROs:** • St. George's Respiratory Questionnaire (SGRQ).

	• COPD Assessment Test. • Dyspnea Numerical Rating Scale • Exacerbations of Chronic Pulmonary Disease Tool – Patient-Reported Outcome (EXACT-PRO) (which includes the Evaluating Respiratory Symptoms in COPD [E-RS: COPD] subscales of the EXACT-PRO) at randomization and every evening following day of randomization. • Inhalations of short-acting rescue medications. **Healthcare Resource Utilization and Economics:** • Reasons and duration of hospitalizations and ED visits. • Length (hours) of stay in ED per visit. • Unscheduled visits for urgent care primarily related to COPD symptoms. • Total length (hours) of stay in ED over the 28-day Treatment Assessment Period. • ICU admission rate. • Time to ready-for-discharge in hospitalized participants based on clinical assessment and lung function tests.
Safety:	Safety will be evaluated by assessment of reported adverse events (AEs), including serious adverse events (SAEs) and AEs of special interest (AESIs), drug-induced liver injury (DILI), unanticipated adverse device effects (UADEs), safety laboratory evaluations (hematology, clinical chemistry, and urinalysis), vital signs, physical examinations including injection site evaluation, oxygen saturation detected via pulse oximetry, ECG, and concomitant medication/treatment review.
Immunogenicity:	Immunogenicity will be evaluated by assessment of anti-drug antibodies (ADAs) and, if applicable, neutralizing antibodies (nAbs).
Pharmacokinetics (PK):	Blood samples for PK assessments will be collected prior to administration of IP and post-dose at the specified timepoints. Plasma samples for determination of rademikibart concentrations will be analyzed by a laboratory using a validated method.
Pharmacodynamics:	Biomarkers of type 2 inflammation will be assessed over the course of the participants' treatment including blood eosinophil count, eotaxin-3, C-reactive protein, total immunoglobulin E, thymus and activation-regulated chemokine. Additionally, pulmonary and activation-regulated chemokine and fibrinogen will be assessed. Fractional exhaled nitric oxide will be measured over the course of the participant's treatment.

Concomitant Medications or Therapies:	**<u>Background Therapy</u>** SoC for the index acute exacerbation is defined for this protocol as treatment with oral/systemic corticosteroid[s] (prednisone 40 mg/day or equivalent) for 5 days with or without antibiotic(s) for 7 days; the modification of the dose and/or duration of prednisone (40 mg/day or equivalent) and/or the antibiotic is not recommended but may be allowed according to the Investigator's/medically qualified designee's judgement. The start of SoC is defined as the start of either oral or systemic corticosteroids(s) or antibiotic(s), whichever is earliest. Note: SoC must be documented in the participant's source documentation and in the electronic Case Report Form (eCRF). The use of other medications for treatment of the index acute COPD exacerbation and any subsequent COPD exacerbation(s), if applicable, is at the discretion of the Investigator or medically qualified health care personnel. Use of medication for treatment of subsequent exacerbations does not need to follow the SoC requirements for the index acute exacerbation. In addition, participants are instructed to continue their regular COPD maintenance treatments for the duration of the trial. Other concomitant COPD maintenance medications may be allowed at the discretion of the Investigator following consultation with the Sponsor Medical Monitor or designee, except for short-acting anticholinergics for use as rescue medication. Oxygen for intermittent use or PRN therapy ≤15 hours per day is allowed. LTOT or nocturnal oxygen therapy required for >15 hours are excluded throughout the trial.
Sample Size Determination:	To account for a 5% dropout rate, approximately 160 participants will be randomized to ensure that 152 participants are evaluable. Assuming a 22.5% treatment failure rate for the rademikibart group and 45% treatment failure rate in the placebo group up to 28 days after randomization, this sample size will provide at least 80% power to detect a difference, using a two-sided Type I error rate of 5%. Conditional power will be calculated during the IA and the final sample size will be defined according to the prespecified rules.
Statistical Methods:	Complete details of the statistical analyses and methods, including data conventions, will be contained in a Statistical Analysis Plan. Descriptive statistics will be used to summarize the safety, PK, and PD data. Demographics and other baseline characteristics will be listed and summarized. One IA is planned to be performed when approximately 80 participants with an acute COPD exacerbation have completed the Week 4 Visit. During the IA, the treatment failure rate will be assessed, the COPD exacerbation rate over the 4-week period will be assessed, and conditional power will be calculated by an independent statistician. The independent

	statistician will compare the calculated conditional power with the prespecified sample size to determine the final sample size for the trial. The independent statistician and Data Monitoring Committee (DMC) will recommend to the Sponsor any changes required to the sample size. Results from the IA will be communicated to a limited number of the Sponsor's senior management team independent of the clinical trial team; these people will be identified in the unblinding plan before the IA are performed. **Efficacy:** Cochran-Mantel-Haenszel chi-square tests will be used to compare treatment groups with respect to the proportion-based binary efficacy endpoints and a mixed model repeated measures or analysis of covariance will be used to compare treatment groups with respect to continuous efficacy endpoints. The rate of moderate and severe COPD exacerbations in the 28 days after randomization will be analyzed using a negative binomial regression model adjusting for randomization stratification factors and baseline characteristics. The time to first moderate or severe COPD exacerbation will be analyzed using a stratified log-rank test. **Safety:** Safety data will be summarized using frequency tables (counts with percentages) and will be presented by treatment and scheduled time, if appropriate. AEs will be classified by Medical Dictionary for Regulatory Activities. Continuous safety data will be summarized using descriptive statistics by treatment and scheduled visits and timepoints, if applicable. **PK:** Individual plasma concentrations will be plotted and summarized using descriptive statistics. **PD:** Changes of serum levels of PD analytes and peripheral eosinophil counts will be summarized using descriptive statistics by treatment and scheduled time and, if appropriate, will be plotted by treatment. **Immunogenicity:** Incidence and duration of treatment-emergent ADAs and nAbs will be summarized by treatment group.
Data Monitoring/Other Committee:	An independent DMC comprising members who are independent of the Sponsor and Investigators will be established for this trial. This committee will include externally based individuals with expertise in the diseases under trial, biostatistics, and/or clinical research. The primary responsibilities of the DMC are to review and evaluate the safety data during the trial, review IA results and make appropriate recommendations regarding the conduct of the clinical trial to the Sponsor. The DMC will also provide the Sponsor with appropriate recommendations on the conduct of the clinical trial to ensure the protection and safety of the participants enrolled in the trial. The DMC will also institute any measures that may be required for ensuring the integrity of the trial results during the trial execution.

	All activities and responsibilities of the DMC are to be described in the DMC charter. An Independent Adjudication Committee will be constituted to provide an independent, external, systematic and unbiased assessment of blinded data to confirm the diagnosis of Investigator-reported non-fatal myocardial infarction, non-fatal stroke (hemorrhagic, ischemic, embolic), as well as cardiovascular deaths during the trials. Adjudication Committee members' responsibilities and the process for data review are to be described in the Adjudication Committee Charter.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this protocol.

Table 1: List of Abbreviations

Abbreviation or Specialist Term	Explanation
AD	atopic dermatitis
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the concentration-time curve
β-hCG	beta-human chorionic gonadotropin
BD	bronchodilator
BP	blood pressure
CAT	COPD assessment test
CFB	change-from-baseline
CFR	Code of Federal Regulations
C_{max}	maximum concentration
CONSORT	Consolidated Standards or Reporting Trials
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CPK	creatinine phosphokinase
CRO	contract research organization
CRP	C-reactive protein
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CV	curriculum vitae
DILI	drug-induced liver injury

Abbreviation or Specialist Term	Explanation
DMC	Data Monitoring Committee
e-diary	electronic diary
ECG	electrocardiogram
eCRF	electronic Case Report Form
ED	emergency department
EDC	electronic data capture
EMA	European Medicines Agency
EOT	End of Trial
E-RS	Evaluating Respiratory Symptoms
ERS	European Respiratory Society
EXACT-PRO	Exacerbations of Chronic Pulmonary Disease Tool – Patient-Reported Outcome
FAS	Full Analysis Set
FDA	Food and Drug Administration
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FSH	follicle-stimulation hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPP	Good Publication Practice
HCO_3^-	bicarbonate
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IA	interim analysis
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference for Harmonisation
ICMJE	International Committee of Medical Journal Editors

Abbreviation or Specialist Term	Explanation
ICS	inhaled corticosteroid
ICU	intensive care unit
ID	identification
IEC	Independent Ethics Committee
IL	interleukin
IND	Investigational New Drug
IP	investigational product
IRB	institutional review board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
KD	dissociation constant
LABA	long-acting β2-adrenergic agonists
LAMA	long-acting muscarinic antagonists
LDH	lactate dehydrogenase
LTOT	long-term oxygen therapy
MDI	metered dose inhaler
nAb	neutralizing antibody
NOAEL	no-observed-adverse-effect level
NRS	Numerical Rating Scale
PARC	pulmonary and activation-regulated chemokine
PDE	phosphodiesterase
PEF	peak expiratory flow
PFS	pre-filled syringe
PK	pharmacokinetic(s)
PKS	Pharmacokinetic Analysis Set
PPS	Per-Protocol Analysis Set
PRN	pro re nata, as needed
PRO	patient-reported outcome
PT	preferred term
q2w	every 2 weeks

Abbreviation or Specialist Term	Explanation
QTcF	QT interval corrected for heart rate using Fridericia's formula
Rα	receptor alpha
RBC	red blood cell
RCT	randomized controlled trial
RS	Randomized Set
SABA	short-acting β-agonist
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SGRQ	St. George's Respiratory Questionnaire
SoA	Schedule of Assessments
SoC	standard of care
SS	Safety Analysis Set
STAT6	signal transducer and activator of transcription 6
SUSAR	suspected unexpected serious adverse reaction
TARC	thymus and activation-regulated chemokine
TEAE	treatment-emergent adverse event
UADE	unanticipated adverse device effect
ULN	upper limit of normal
US/USA	United States/United States of America
VBG	venous blood gas
VCAM	vascular cell adhesion molecule
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

4. INTRODUCTION

4.1. Background

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms, such as breathlessness (or dyspnea), cough, sputum production, and progressive airflow limitation. This is typically caused by airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases [Global Initiative for Chronic Obstructive Lung Disease (GOLD 2024)]. Cigarette smoke is the primary cause of COPD and is responsible for approximately 70% of COPD cases (Barnes 2019; GOLD 2024). Other risk factors for COPD are air pollution including nanoparticles, occupational exposure, respiratory infections, childhood asthma, and alpha-1 antitrypsin deficiency (GOLD 2024). COPD is a major cause of disability, morbidity, and mortality, resulting in millions of deaths annually worldwide and contributing significantly to health care costs. It is a main global epidemic increasing as populations age, is the third leading cause of death worldwide, affecting approximately 10% of subjects ≥45 years (GOLD 2024). In the United States (US), COPD is the sixth leading cause of death in United States (American Lung Association 2021).

COPD is a heterogeneous and complex disease with various endo-phenotypes and clinical presentations. The pathological hallmarks of COPD are inflammation of the small airways (bronchiolitis) and destruction of lung parenchyma (emphysema) (Cosio Piqueras and Cosio 2001). It is a complex condition that involves the activation of multiple inflammatory cells, such as lymphocytes, neutrophils, macrophages, and eosinophils, which contribute to the inflammatory response (Barnes 2018; Agustí and Hogg 2019). A subgroup of COPD patients (~20 to 40%) have been identified who are characterized by a concomitant elevation in blood eosinophils, suggesting a type 2 inflammatory component of the disease (Leigh et al. 2006; Saha and Brightling 2006; Singh et al. 2014).

Type 2 inflammation is a specific pattern of immune response that exists across a spectrum of atopic diseases. Interleukin (IL)-4 and IL-13 are key drivers of type 2 inflammation and signal through the shared receptor IL-4 receptor alpha (Rα), expressed by airway epithelial cells as well as innate and adaptive immune cells. IL-4 and IL-13 promote activation and trafficking of type 2 inflammatory cells, including eosinophils, to the lungs via the release of chemoattractants, in particular eotaxin-3 (also known as eosinophil chemotactic protein), from airway epithelial cells (Ghebre et al. 2018; George et al. 2020). Eosinophils play a crucial role in type 2 inflammation, contributing to airway damage and heightened immune responses. In COPD, their presence reflects a mixed inflammatory pattern distinct from the neutrophilic inflammation traditionally associated with the disease. This eosinophilic involvement has been linked to a greater predisposition to exacerbations, likely due to increased airway reactivity and susceptibility to environmental triggers. By targeting this pathway with inhaled corticosteroid (ICS), the frequency and severity of exacerbations can be significantly reduced, highlighting the importance of peripheral eosinophil counts as both a diagnostic tool and a guide for personalized treatment strategies in COPD. Peripheral eosinophilia (≥300 cells/µL), a marker of type 2 inflammation, defines a clinically significant subgroup of COPD patients characterized by a higher risk of exacerbations (Yun et al. 2018) and this eosinophilic phenotype is gaining recognition as an important treatable trait. Elevated eosinophil levels not only signal a distinct

inflammatory pathway but also serve as a predictive biomarker for identifying patients who are more likely to benefit from ICS therapy in association with inhaled bronchodilators (BDs), long-acting β2-adrenergic agonists (LABA) and long-acting muscarinic antagonists (LAMA) (GOLD 2024).

Biologics targeting type 2 cytokines and epithelial-derived alarmins are currently under development for targeted therapy of COPD with type 2 inflammation. Several randomized clinical trials (RCTs) have evaluated the efficacy of biologics targeting IL-5 (benralizumab, mepolizumab) and IL-4Rα (dupilumab), in COPD. Dupilumab, an IL-4Rα blocker, was recently approved by the Food and Drug Administration (FDA) as an add-on maintenance treatment of adult patients with inadequately controlled COPD and an eosinophilic phenotype (Dupixent USPI 2024). The BOREAS (NCT03930732) and NOTUS (NCT04456673) studies evaluated the efficacy of dupilumab in COPD patients with a blood eosinophil count of ≥300 cells/μL and experiencing exacerbations despite standard triple therapy (LABA, LAMA, and ICS). Dupilumab treatment resulted in 30% and 34% reduction in annualized rate of exacerbations, improved both lung function and COPD symptoms, and improved quality of life (Bhatt et al. 2023; Bhatt et al. 2024) These trials represent the significant progress that has been made in prevention of COPD exacerbations using maintenance treatment with monoclonal antibody therapy. However, there have been relatively few trials examining the treatment of an acute COPD exacerbation with biologics (Nowak et al. 2015; Ramakrishnan, Russell, et al. 2024).

COPD exacerbation is a sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variations, necessitating a change in regular medication in a patient with underlying COPD (Celli et al. 2021). These acute exacerbations, often triggered by infections or environmental factors (Miravitlles et al. 2012), which tend to occur in clusters, increase with disease severity (Hurst et al. 2009), and come with high societal and economic burdens. In the US, COPD exacerbations account for over 1.5 million emergency department (ED) visits annually, with a substantial portion leading to hospital admissions (Centers for Disease Control and Prevention (CDC) 2023). Current treatments at the time of a COPD exacerbation are limited to systemic glucocorticoids, antibiotic therapy, or both, and are not wholly adequate with evidence restricted to only a few clinical trials (Walters et al. 2014). Additionally, these treatments are associated with adverse effects (Barnes 2010), and approximately 20% of patients hospitalized for acute COPD exacerbations are readmitted to hospital within 30 days (Shah et al. 2015). New treatment intervention during acute exacerbation that could reduce the risk of recurrent exacerbation is one of the greatest unmet needs in the management of COPD.

4.2. Summary of Benefits and Risks of Rademikibart

Rademikibart (also known as CBP-201) is a novel, potent, and selective recombinant human monoclonal antibody directed against the human cell surface protein IL-4Rα, a common subunit of the IL-4 and IL-13 (IL-13) receptor dimers. Connect Biopharmaceuticals, Ltd, Connect Biopharm LLC and affiliates (collectively referred to here as Connect) is developing rademikibart for the treatment of respiratory diseases with Type-2 inflammation.

4.2.1. Nonclinical Experience

Extensive in vitro, ex vivo, and in vivo studies have been conducted to characterize the pharmacological properties of rademikibart. Rademikibart bound recombinant soluble monomeric human IL-4Rα has a dissociation constant (KD) of approximately 20.7 pM. It does not bind to mouse or monkey IL-4Rα. Rademikibart inhibits proliferation of TF-1 cells stimulated with IL-4 and IL-13 with a half-maximal inhibitory concentration (IC_{50}) of 8.00 and 9.68 ng/mL, respectively. It also inhibits IL-4- and IL-13-mediated signal transducer and activator of transcription 6 (STAT6) activation in HEK-Blue IL-4/IL-13 secreted alkaline phosphatase cells; with an IC_{50} of 7.04 and 6.56 ng/mL, respectively. In ex vivo assays, rademikibart inhibited IL-4-induced production of thymus and activation-regulated chemokine (TARC) in human peripheral blood mononuclear cells, and the IC_{50} was 59.1 ng/mL. These studies show that rademikibart is a highly potent antibody against the IL-4Rα. No rademikibart-related adverse effects or changes on the central nervous, cardiovascular, respiratory, and lymphoid systems were found following subcutaneous (SC) administration of up to 200 mg/kg/week of rademikibart in cynomolgus monkeys.

The off-target toxicity of rademikibart was evaluated in a 4-week Good Laboratory Practice (GLP) study in cynomolgus monkeys. Rademikibart (6, 40, and 200 mg/kg) was administered once a week by SC injection and was very well tolerated at all dose levels. No abnormal clinical observations or abnormalities in hematology, clinical chemistry, or pathology were noted. No abnormalities in cardiac and lung function were observed. Based on this study, the no-observed-adverse-effect level (NOAEL) was 200 mg/kg, the highest dose tested, which corresponds to a maximum concentration (C_{max}) of approximately 6279 μg/mL and an area under the concentration-time curve at the last time point (AUC_{last}) of approximately 837.4 h•mg/mL.

With the availability of the transgenic mice that express human IL-4 and IL-4Rα, a GLP 26-week toxicity study of rademikibart with a 4-week recovery period in B-hIL4/hIL4RA mice by SC injection was conducted. No abnormal clinical observations or abnormalities in pathology were found. Findings in hematology and clinical chemistry at 200 mg/kg on Day 184 that were considered to likely be test article related due to its pharmacological effect as a monoclonal antibody included decreases in absolute count of lymphocytes and white blood cells in males and an increase in serum globulin and a decrease in albumin/globulin females and males. Under the conditions of the study, the NOAEL was considered to be 200 mg/kg, the highest dose tested, which corresponds to a C_{max}, $AUC_{0\text{-}168h}$, and estimated AUC_{inf} of rademikibart on Day 176 of 5000 μg/mL, 586 h•mg/mL, and 1940 h•mg/mL, respectively, in males; and 4250 μg/mL, 509 h•mg/mL, and 900 h•mg/mL, respectively, in females.

4.2.2. Clinical Experience

Rademikibart has been evaluated in 3 Phase 1 studies in healthy adults, one Phase 1b trial in participants with atopic dermatitis [AD]), and 5 Phase 2 studies (3 in participants with AD, 1 in participants with asthma, and 1 in participants with nasal polyps). Phase 1 studies demonstrated that rademikibart is safe and well-tolerated, with no treatment-related serious adverse events (SAEs) and only mild-to-moderate treatment-emergent adverse events (TEAEs).

In Phase 2 studies, rademikibart showed potential as an effective and safe treatment for AD, asthma, and nasal polyps. It significantly improved disease severity and symptom control, with a

safety profile comparable to placebo. Most TEAEs were mild-to-moderate, and no SAEs related to rademikibart were reported.

In a single-ascending dose trial involving 40 healthy adult participants, single SC doses of rademikibart (75 mg, 150 mg, 300 mg, 600 mg) or placebo were administered, with an additional cohort administered a 30-minute intravenous infusion of 300 mg rademikibart or placebo. Rademikibart exposure following SC dosing increased in a greater-than-dose-proportional manner, indicating a nonlinear component to clearance. The absolute bioavailability was 58%, and the median time to the last detectable drug concentration ranged from 14 days at 75 mg to 56 days at 600 mg. Single SC doses significantly reduced serum TARC levels, a biomarker in AD and other inflammatory conditions. As shown in this trial, a single 600 mg SC dose results in substantially higher rademikibart exposure up to 28 days relative to the other SC dose levels, with all dose levels similarly well tolerated.

A comparative bioavailability trial conducted in healthy adults, comparing SC dosing of rademikibart 300 mg administered from a pre-filled syringe (PFS) relative to the same dose administration from a vial, indicated pharmacokinetic (PK) similarity of the 2 product presentations.

In a Phase 2 efficacy and safety clinical trial (CBP-201-WW002) of rademikibart as an add-on treatment to adult participants with persistent moderate-to-severe asthma not adequately controlled with medium to high dose ICS/LABA therapy, participants were randomized to receive rademikibart (a 600 mg loading dose followed by 300 mg or 150 mg rademikibart every 2 weeks [q2w]) or placebo SC for 24 weeks. Rademikibart demonstrated significant improvements in lung function, as measured by pre-bronchodilator (pre-BD) forced expiratory volume in 1 second (FEV_1). Compared to placebo, both rademikibart treatment groups (150 mg SC q2w and 300 mg SC q2w) resulted in significant improvement in pre-BD FEV_1, which started as early as Week 1 and was sustained through Week 24 compared. A prospectively planned analysis showed further improvements in lung function in participants with eosinophil levels ≥300 cells/µL. A greater reduction in both rademikibart groups compared with the placebo group in Asthma Control Questionnaire score (Q1-5 +7) (indicating improved asthma control) was observed at Week 24, with decreases in the rademikibart groups as early as Week 1. Although not powered to detect differences in exacerbations, the trial showed that treatment with rademikibart was associated with a reduction in exacerbations compared with placebo. The safety profile was favorable, with no deaths or SAEs related to rademikibart reported.

In addition, a post hoc analysis was performed to evaluate efficacy in a subset of COPD-like patients defined as having asthma onset age >40 years and a post-bronchodilator (post-BD) FEV_1)/forced vital capacity (FVC) ratio of <0.7 at the Screening Visit. Pre-BD FEV_1 in COPD-like patients at Week 12 was improved over Baseline with both rademikibart doses, and improvement was achieved in patients with eosinophil levels of ≥300 cells/µL. Improvements began in Week 1 (both doses) and were sustained through 24 weeks of treatment in both the overall COPD-like population and in those with eosinophils ≥300 cells/µL. This analysis combined with recent IL-4/COPD data (Bhatt et al. 2023; Bhatt et al. 2024) supports the further examination of rademikibart in the targeted eosinophilic-driven COPD trial population.

Based on results from population PK analysis that included data from participants in the age range of 15-74 years who received rademikibart in studies of atopic dermatitis, age was not a

significant covariate for the PK parameters according to covariate screening results. Therefore, no dose adjustment is required for adult participants of different ages.

Additional details, as well as details on additional studies conducted with rademikibart, are available in the rademikibart Investigator's Brochure (IB).

4.3. Rationales

4.3.1. Rationale for Clinical Development

IL-4Rα plays a central role in the activation of allergic inflammation by mediating the functions of both IL-4 and IL-13. Preclinical studies have demonstrated that inhibition of IL-4Rα is effective in ameliorating allergic inflammation in animal models, suggesting that blocking this receptor will have the potential to treat a broad range of allergic inflammatory diseases (Beckmann et al. 1990). Clinical studies of the IL-4Rα antibody dupilumab have shown strong efficacy in a number of allergic disease conditions, including AD, asthma, and COPD (Dupixent EU SmPC 2024; Dupixent USPI 2024).

Patients with asthma and COPD have an ongoing need for safe, effective, and convenient therapies for the treatment of these allergic inflammatory conditions. Blockade of IL-4Rα has been validated as a useful target in treatment of multiple chronic respiratory diseases, including asthma and COPD with type 2 inflammation.

4.3.2. Rationale for Trial Conduct

COPD exacerbations account for a significant proportion of COPD-related and total health care costs. They are associated with an accelerated decline in lung function, health status, and increased risk for mortality with the cumulative risk for a next exacerbation or mortality increasing with each successive exacerbation (Donaldson 2006; Suissa et al. 2012). Given the high prevalence and burden of exacerbations of COPD, there is an unmet need for novel therapies that can treat moderate-to-severe COPD exacerbations more effectively by reducing the duration and preventing recurrent exacerbations in the following 30 to 90 days.

Benralizumab binds with high affinity to IL-5Rα, which is expressed on the surface of eosinophils and basophils and induces rapid and sustained depletion of eosinophils in the lung. A post hoc analysis of the Phase 3 RCTs GALATHEA (NCT02138916) and TERRANOVA (NCT02155660) identified a potential responder population (≥3 COPD exacerbations in the previous year with blood eosinophils ≥300 cells/μL who had ≥1 exacerbation following randomization despite treatment) in which treatment with benralizumab as an add-on treatment to standard dual inhaled maintenance therapy, prevented recurrent COPD exacerbations during 30- and 90-day periods following an initial exacerbation, a vulnerable period for an exacerbation to occur (Singh et al. 2023).

Recently, the Acute Exacerbations Treated With BenRAlizumab (ABRA) trial (NCT04098718) further evaluated blood eosinophil-guided benralizumab therapy in COPD patients with eosinophilic exacerbations (blood eosinophils ≥300 cells/μL in the acute setting). At 90 days, a single SC injection of benralizumab, with or without a short course of systemic glucocorticoids reduced treatment failures, prolonged time to first event, and improved respiratory symptoms and disease-specific health quality compared with standard care with oral corticosteroids following an exacerbation (Ramakrishnan, Russell, et al. 2024). This is a promising finding, as recurrent

COPD exacerbations carry serious risks for patients, including hospital readmittance 30 to 90 days following an event (Alqahtani et al. 2021; Stolz et al. 2022), inpatient mortality of 10%, and up to 50% all-cause mortality 2 years after an event (Stolz et al. 2022). These results demonstrate the importance of eosinophils in COPD despite the fact that benralizumab added to inhaled maintenance treatments did not significantly reduce the annual COPD exacerbation rate after 56 weeks (Criner et al. 2019) in patients characterized by an eosinophilic phenotype (eosinophils ≥220 cells/μL, primary analysis population).

Dupilumab, targeting IL-4 and IL-13, affects eosinophil trafficking to the lung by inducing the overexpression of the vascular cell adhesion molecule 1 (VCAM-1). VCAM-1 is involved in the recruitment of eosinophils from the bloodstream to the lungs through its interaction with α4-integrin. This process facilitates the movement of eosinophils to the lung tissue, contributing to the inflammatory response in respiratory diseases. In contrast to benralizumab, The BOREAS and NOTUS trials demonstrated that dupilumab treatment significantly reduced both annualized exacerbation rates and improved lung function in COPD patients with eosinophilic phenotype (eosinophils ≥300 cells/μL) (Bhatt et al. 2023; Bhatt et al. 2024). Although blood eosinophil counts serve as practical and accessible markers of type 2 inflammation, type 2 inflammatory pathways are not necessarily driven solely by blood eosinophils. The efficacy that was observed in the BOREAS and NOTUS trials is supported by the central role of IL-4 and IL-13 in driving airway epithelial barrier dysfunction, airway remodeling, and, more specifically for IL-13, goblet-cell hyperplasia and mucus secretion in type 2 mediated airway diseases (Maspero et al. 2022; Rabe et al. 2023). Collectively, these findings highlight the importance of targeting IL-4 and IL-13 as drivers of type 2 inflammation in COPD.

Based on the available evidence in COPD patients with an eosinophilic phenotype, it is anticipated that a fully human monoclonal antibody that blocks the shared receptor component for IL-4 and IL-13, key and central drivers of type 2 inflammation, could acutely treat eosinophilic exacerbations of COPD. However, this approach has not yet been tested. Given the recent promising findings in patients with eosinophilic exacerbations from the ABRA trial (Ramakrishnan, Russell, et al. 2024), the rapid improvements in lung function with rademikibart (Kerwin et al. 2024), as well as the significant unmet medical needs in treating a COPD exacerbation, it is worth investigating whether eosinophilic exacerbations of COPD could be treated acutely with rademikibart.

Rademikibart has demonstrated efficacy and safety across various diseases associated with type 2 inflammation including asthma. In the Phase 2 trial in patients with persistent asthma, participants treated with rademikibart demonstrated significant improvements in lung function by Week 1 and was sustained through Week 24, as measured by in-clinic spirometry. A subgroup analysis of “COPD-like” patients (eg, patients with age of onset asthma >40 years and post-BD FEV_1/ FVC 0.7) showed similar treatment effects compared to the overall population.

In an exploratory post-hoc analysis of this trial, the absolute change from baseline (CFB) in pre-BD FEV_1, derived from self-administered at-home spirometry on Days 1 through 7, was analyzed in participants with baseline eosinophil counts ≥300 cells/μL. In this subpopulation, 77% of the Week 1 improvement in pre-BD FEV_1 was achieved within 24 hours post-dose (FEV_1 CFB: 93 mL improvement vs -101 mL for placebo), with 84% of the total improvement realized by Day 2. This post hoc analysis demonstrates that rademikibart delivers rapid and significant lung function improvement, with notable gains within 24 hours of a single 600 mg loading dose.

These findings highlight rademikibart's potential as a fast-acting, effective therapy for type 2 inflammation-driven airway disease and suggest its possible utility in early treatment following acute exacerbations of asthma or COPD.

4.3.3. Rationale for Trial Design

This Phase 2 trial is designed to evaluate the efficacy and safety of a single 600 mg SC dose of rademikibart as adjunct therapy to standard therapy in adult participants with COPD characterized by an eosinophilic phenotype (peripheral blood eosinophil counts of ≥300 cells/µL at Screening Visit 1b or as part of the assessment of the index acute COPD exacerbation within 72 hours prior to Screening) who require urgent healthcare treatment for an acute COPD exacerbation. A randomized, placebo-controlled trial design where the effect of the investigational product (IP) is assessed on top of the standard therapy is considered to be the most appropriate design to explore the efficacy and safety of a novel biologic therapy in COPD exacerbation. Similar trial designs and endpoints have been employed for recent trials with other biologics and small molecule drugs in acute exacerbation (Fahy et al. 2021; Ramakrishnan, Russell, et al. 2024). In addition, this trial intends to assess the PK profile of rademikibart in the trial population.

The primary endpoint of treatment failure rate has been widely used in interventional clinical trials in COPD exacerbations (de Jong et al. 2007; Ramakrishnan, Jeffers, et al. 2024; Ramakrishnan, Russell, et al. 2024).The proposed primary endpoint would support the investigation of the hypothesis that rademikibart reduces the treatment failure rate for index acute COPD exacerbations during the vulnerable period in the targeted trial population: those experiencing an acute COPD exacerbation with high eosinophil counts and a history of exacerbations. This trial is also designed to evaluate the efficacy of rademikibart compared to placebo as an adjunct to standard therapy on subsequent COPD exacerbations in the targeted trial population.

4.3.4. Rationale for Comparator

Placebo has been chosen as the control group as there is no biologic approved for the treatment of acute exacerbations of COPD. There is no anticipated risk for participants randomized to the placebo group, as all participants will receive the standard therapy for the acute COPD exacerbation, including oral/systemic corticosteroids (prednisone 40 mg/day or equivalent), antibiotics, and/or other medical interventions at the discretion of the Investigator or a medically qualified designee. In addition, participants are instructed to continue their regular COPD maintenance treatments throughout the trial.

4.3.5. Rationale for Trial Population

This trial targets participants with COPD characterized by an eosinophilic phenotype who are experiencing an acute exacerbation and are at high risk for future exacerbations. This represents a population with significant unmet medical need in this disease who will potentially benefit from this trial.

The clinical trial population includes adult participants with COPD with an eosinophilic phenotype, with an appropriate age range of 40 to 80 years, inclusive, and history of a COPD exacerbation requiring the use of systemic corticosteroids in the previous year. Participants in

this trial must experience an acute COPD exacerbation with a blood eosinophil counts of ≥300 cells/µL and required systemic corticosteroids as standard of care (SoC) treatment in the urgent healthcare setting for the current acute COPD exacerbation.

Patients with eosinophilic COPD exacerbations, characterized by blood eosinophil counts of ≥300 cells/µL, have a higher frequency of hospital readmissions and new exacerbations within one year (Hasegawa and Camargo 2016). Dupilumab, as a maintenance therapy, has shown robust and consistent clinical efficacy in patients with COPD exhibiting evidence of type 2 inflammation, guided by blood eosinophil counts of ≥300 cells/µL at Screening. This raises the possibility that rademikibart could be an effective therapy in the acute setting for patients with an eosinophilic COPD exacerbation characterized by blood eosinophil counts of ≥300 cells/µL.

4.4. Compliance

The trial site is required to adhere to all applicable laws, regulations, and guidelines including, but not limited to, the US Code of Federal Regulations (CFR), International Conference for Harmonisation (ICH), Health Insurance Portability and Accountability Act (HIPAA) of 1996, Good Radiation Practice, as well as any applicable local and federal regulations.

4.4.1. Regulatory Safety Reporting Requirements

The Investigator must promptly report to the Sponsor all serious adverse events (SAEs), unanticipated adverse device effects (UADEs), adverse events of special interest (AESIs), and suspected drug-induced liver injury (DILI) events as defined in accordance with the procedures detailed in in Section 11.7. The Sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification by the Investigator of urgent safety reports as described in Section 11.7 to meet legal obligations and ethical responsibilities regarding the safety of other participants is required.

Investigator letters are prepared according to Sponsor policy and are forwarded to the Investigators as necessary. An Investigator letter is prepared for any suspected adverse reaction that is attributable to IP, that is both serious and unexpected. The purpose of the Investigator letter is to fulfill specific regulatory and Good Clinical Practice (GCP) requirements regarding the product under investigation.

The Investigator, or responsible person according to local requirements, must comply with requirements related to the reporting of SAEs to the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

The Sponsor is responsible for informing IRBs/IECs, Investigators, and regulatory authorities of findings that could adversely affect the safety of participants or affect the conduct of the trial. Events will be reported to regulatory authorities in accordance with expedited and periodic reporting requirements.

4.4.2. Unanticipated Problems

Unanticipated problems are incidents, experiences, or outcomes that **meet all of the following criteria**:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the research protocol and informed consent document approved by the IRB/IEC and (b) the characteristics of the participant population being studied.
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggest that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Only a small subset of adverse events (AEs) occurring in trial participants will meet these 3 criteria for an unanticipated problem. The following single occurrences of AEs should be considered as unanticipated problems that must be reported to the IRB/IEC:

- A unexpected SAE that is uncommon and strongly associated with drug exposure (such as angiodema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
- A unexpected SAE that is not commonly associated with drug exposure, but uncommon in the trial population (eg, tendon rupture, progressive multifocal leukoencephalopathy).
- An AE that is described or addressed in the IB, protocol, or ICF documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in trial participants,

Refer to Section 11.3.2 for definition of an SAE and Section 11.3.6 for the definition of unexpected.

Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of clinical trials that represent unanticipated problems but are not considered AEs. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with AEs (eg, theft of a trial laptop that included individually identifiable sensitive information about a trial participant). In other cases, unanticipated problems place participants or others at increased *risk* of harm, but no harm occurs (eg, a dosing error increased the risk of toxic manifestations of the IP, but the participant experienced no AE).

If the Investigator determines that an event meets the definition of an unanticipated problem, he/she must notify the Sponsor or designee **within 24 hours** of the Investigator becoming aware of the problem.

The following information will be included with unanticipated problem reporting:

- Protocol identifying information: protocol title, protocol number, and Investigator's name.
- A detailed description of the event, incident, experience, or outcome.
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an unanticipated problem.

It is the Investigator's responsibility to report unanticipated problems to their IRB/IEC, as required by local regulations.

For this multicenter trial, the Investigator may rely on the Sponsor's assessment of unanticipated problems that are based on aggregate analysis of AEs received from multiple clinical trial sites or from other information and provide to the IRB a report of the unanticipated problem prepared by the Sponsor. These include the following:

- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem.
- A small number of occurrences of an unexpected SAE that are not commonly associated with drug exposure, but uncommon in the trial population (eg, tendon rupture, progressive multifocal leukoencephalopathy
- An SAE that is described or addressed in the IB, protocol, or ICF documents, but for which the rate of occurrence in the trial represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison).
- Any other AE or safety finding (eg, based on animal or epidemiologic data) that would cause the Sponsor to modify the IB, trial protocol, or ICF documents, or would prompt other action by the IRB/IEC to ensure the protection of human subjects.

4.4.3. Protocol Deviations

A protocol deviation is any modification to protocol-specified procedures, whether intentional or not, that occur without prior IRB/IEC approval and submission to regulatory authority(ies) of the protocol amendment implementing the modification. The Investigator will not implement any protocol modification without prior approval of the IRB/IEC and agreement by the Sponsor except where necessary to eliminate an apparent immediate hazard to trial participants.

Protocol deviations fall into 2 categories:

- Important Protocol Deviations.
- Other Protocol Deviations.

Important Protocol Deviations are deviations that might significantly affect the completeness, accuracy, and/or reliability of the trial data or that might significantly affect a participant's rights, safety, or well-being. Some examples include:

- Failure to conduct trial procedures designed to assess participant safety or failure to adequately monitor participants.
- Administration of concomitant treatment prohibited by the protocol that may increase risks to participants and/or impact interpretation of safety and efficacy.
- Failure to obtain informed consent or meet other applicable requirements for the protection of human participants.
- Failure to protect a participant's identifiable private protected health information.

- Enrollment of a participant in violation of key eligibility criteria designed to ensure a specific participant population.
- Failure to administer the IP according to specifications in the protocol, administration of the wrong treatment or incorrect dose to participants.
- Failure to collect data to evaluate important trial endpoints (eg, primary or secondary endpoints).
- Premature unblinding of a participant's treatment allocation for reasons other than those specified in the protocol.
- Failure to withdraw IP administration from participants who meet withdrawal criteria.

Other Protocol Deviations are those that do not meet the definition of an Important Protocol Deviation. Some examples of all Other Protocol Deviations include small deviations from protocol-specified visit windows; a signed consent missing a participant's initials on a page; or failure to perform a trial procedure not relevant for safety monitoring or not related to an important trial efficacy endpoint (eg, primary or secondary endpoints).

For any protocol deviation, the Investigator will document it in the participant's source documents, indicating if any are an Important Protocol Deviation, and notify the Sponsor or designee. The Investigator will discuss the Important Protocol Deviation with the Sponsor's Medical Monitor or designee to reach an agreement on whether the participant should be withdrawn from the trial. The Investigator will notify the IRB/IEC of Important Protocol Deviations, as required by IRB/IEC guidelines and site requirements. The Sponsor is responsible for notifying the regulatory authorities, if required.

4.4.4. Regulatory Authority Approval

The Sponsor will obtain approval to conduct the trial from the appropriate regulatory agency in accordance with any applicable country specific regulatory requirements before any site may initiate the trial in that country.

5. OBJECTIVES AND ENDPOINTS

The primary, secondary, and exploratory objectives and endpoints are provided in Table 2.

Table 2: Objectives and Endpoints

Primary Objective	**Primary Endpoint**
• To evaluate the efficacy of rademikibart compared to placebo as an adjunct to standard therapy on the treatment failure rate within 28 days after randomization in participants with COPD and an eosinophilic phenotype experiencing an acute COPD exacerbation.	• Treatment failure rate within 28 days after randomization.
Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of rademikibart compared to placebo as an adjunct to standard therapy on subsequent COPD exacerbations in participants with COPD and an eosinophilic phenotype experiencing an acute COPD exacerbation.	• Rate of new moderate and severe COPD exacerbations over the 28 days after randomization. • Time to the first new moderate or severe COPD exacerbation in the 28 days after randomization. • Mean CFB in clinical respiratory symptoms of COPD using the E-RS: COPD comprised in the EXACT-PRO through Week 1, Week 2, and Week 4. • Absolute CFB in post-BD FEV_1 at Day 3, Week 1, and Week 4.
• To evaluate the safety of rademikibart compared to placebo when administered as an adjunct to standard therapy in participants with COPD and an eosinophilic phenotype experiencing an acute COPD exacerbation.	• Incidence of AEs, including SAEs, AESIs, and DILI reported. • Incidence of UADEs. • Incidence of injection site reactions. • Changes in safety laboratory parameters. • Changes in vital signs, physical examinations, and ECG parameters.
Exploratory Objectives	**Exploratory Endpoints**
• To further evaluate the efficacy of rademikibart compared to placebo as an adjunct to standard therapy on subsequent COPD exacerbations in participants with COPD and an eosinophilic phenotype	• Proportion of participants with at least 1 moderate or severe acute COPD exacerbation (subsequent to the index acute COPD exacerbation) through Week 4 and Week 8.

experiencing an acute COPD exacerbation.	• Rate of moderate and severe COPD exacerbations (subsequent to the index exacerbation) over the 8-week period compared to placebo. • Acute exacerbation rate (all subsequent COPD exacerbations) over the 8-week period compared to placebo.
• To evaluate the incidence of immunogenicity (anti-rademikibart antibodies: ADAs and nAbs) in participants with COPD and an eosinophilic phenotype experiencing an acute COPD exacerbation.	• Incidence and duration of treatment-emergent ADAs and nAbs.
• To evaluate the PK of rademikibart in participants with COPD and an eosinophilic phenotype experiencing an acute COPD exacerbation.	• PK concentrations and, if calculable, PK parameters of rademikibart.
• To evaluate the pharmacodynamics of rademikibart in participants with COPD and an eosinophilic phenotype experiencing an acute COPD exacerbation.	• CFB in FeNO. • CFB in biomarkers in the blood (including but not limited to peripheral blood eosinophil count, eotaxin-3, CRP, total immunoglobulin E, TARC, and PARC).
• To evaluate the effect of rademikibart compared with placebo as an adjunct to standard therapy on lung function in participants with COPD and an eosinophilic phenotype experiencing an acute COPD exacerbation.	• Change from the earliest available measurements in pre-BD FEV_1 (absolute and percent changes, percentage predicted) at Week 1, Week 4, and Week 8. • CFB in post-BD FEV_1 at Day 1 and Day 2, and during the Follow-up Period at Week 8. • CFB or the earliest available measurements in other lung function measurements: pre-BD and post-BD FVC and FEV_1/FVC at scheduled timepoints.
• To evaluate the effect of rademikibart compared with placebo as an adjunct to standard therapy on healthcare resource	• Length of stay in an urgent healthcare facility, ED, or hospital (hours).

utilization in participants with COPD and an eosinophilic phenotype experiencing an acute COPD exacerbation.	• Time to ready-for-discharge in hospitalized participants based on clinical assessment. • Time to ready-for-discharge in hospitalized participants based on VBG results • Total number of COPD-related hospital-stay hours during the first 28 days after discharge from the index acute COPD exacerbation (may include more than 1 COPD-related admission to the hospital). • Total number of COPD-related hospital-stay hours during the 8-week trial period (may include more than 1 COPD-related admission to the hospital). • For hospitalized participants: Hospital readmission rate during the first 28 days after discharge from the index acute COPD exacerbation and during the 8-week trial period. • Total number of all-cause hospital-stay hours during the first 28 days after discharge from the index acute COPD exacerbation (may include more than 1 admission to the hospital). • Total number of all-cause hospital-stay hours during the 8-week trial period (may include more than 1 admission to the hospital). • Incidence and rate of unscheduled visits for urgent care primarily related to COPD symptoms. • Incidence and rate of unscheduled calls for urgent care primarily related to COPD symptoms. • ICU admission rate during the first 4-week trial period. • Invasive ventilation rate during the first 4-week trial period.

• To explore the effect of rademikibart compared with placebo as an adjunct to standard therapy on improvement in symptoms, usage of rescue medications, and health-related quality of life/PROs in participants with COPD and an eosinophilic phenotype experiencing an acute COPD exacerbation.	• CFB in Dyspnea NRS at scheduled timepoints. • Total dose/use of systemic corticosteroids. • Use of daily puffs of rescue medication. • CFB in SGRQ total score compared to placebo at Weeks 4 and 8. • Proportion of participants with SGRQ improvement ≥4 points at Week 4 and Week 8. • CFB in CAT total score compared to placebo at Week 1, Week 4, and Week 8. • Proportion of participants with a decrease from Baseline in CAT total score ≥2 at Week 1, Week 4, and Week 8. • CFB in clinical respiratory symptoms of COPD using the Evaluating Respiratory Symptoms in COPD (E-RS: COPD) comprised in the EXACT-PRO tool during the Follow-up Period at Week 8.

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; BD = bronchodilator; CAT = COPD Assessment Test; CFB = change-from-baseline; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; DILI = drug-induced liver injury; ECG = electrocardiogram; ED = emergency department; E-RS: COPD = Evaluating Respiratory Symptoms in COPD; EXACT-PRO = Exacerbations of Chronic Obstructive Pulmonary Disease Tool- PRO; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ICU = intensive care unit; IgE = immunoglobulin E; nAb = neutralizing antibody; NRS = numerical rating scale; PARC = pulmonary and activation-regulated chemokine; PK = pharmacokinetic(s); PRO = patient-reported outcome; SAE = serious adverse event; SC = subcutaneous; SGRQ = St. George's Respiratory Questionnaire; TARC = thymus and activation-regulated chemokine; UADE = unanticipated adverse device effect; VBG = venous blood gas

6. INVESTIGATIONAL PLAN

6.1. Trial Design

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, interventional trial in participants with an acute COPD exacerbation with type 2 inflammation in the urgent healthcare setting to compare rademikibart plus standard therapy to standard therapy (plus placebo). For the purposes of this trial, an urgent healthcare setting may include an ED, a hospital inpatient ward, or an urgent healthcare facility equipped to provide the level of care specified in this protocol.

The trial is designed to evaluate the efficacy and safety of a single 600 mg SC dose (administered as 4 separate 150 mg injections) of rademikibart as adjunct therapy to standard therapy in adult participants with COPD characterized by an eosinophilic phenotype (peripheral blood eosinophil count of ≥300 cells/µL at Screening Visit 1b or as part of the assessment of the index acute COPD exacerbation within 72 hours prior to Screening) who require urgent healthcare treatment for an acute COPD exacerbation.

This trial will screen participants through 2 different channels:

1. Participants who consent to participate in the trial while in a stable condition, and
2. Participants who consent to participate in the trial at an urgent healthcare visit for acute COPD exacerbation.

Participants who consent to participate through channel 1 will be contacted by telephone approximately every 4 weeks after Screening Visit 1a to collect any changes in concomitant medications and any SAEs. The participant should be reminded to contact the site if they are experiencing worsening symptoms, so the site can determine if they may be experiencing an exacerbation and may qualify for randomization into the trial.

Details on treatment assignment are presented in Section 6.3. A trial schema is provided in Figure 1.

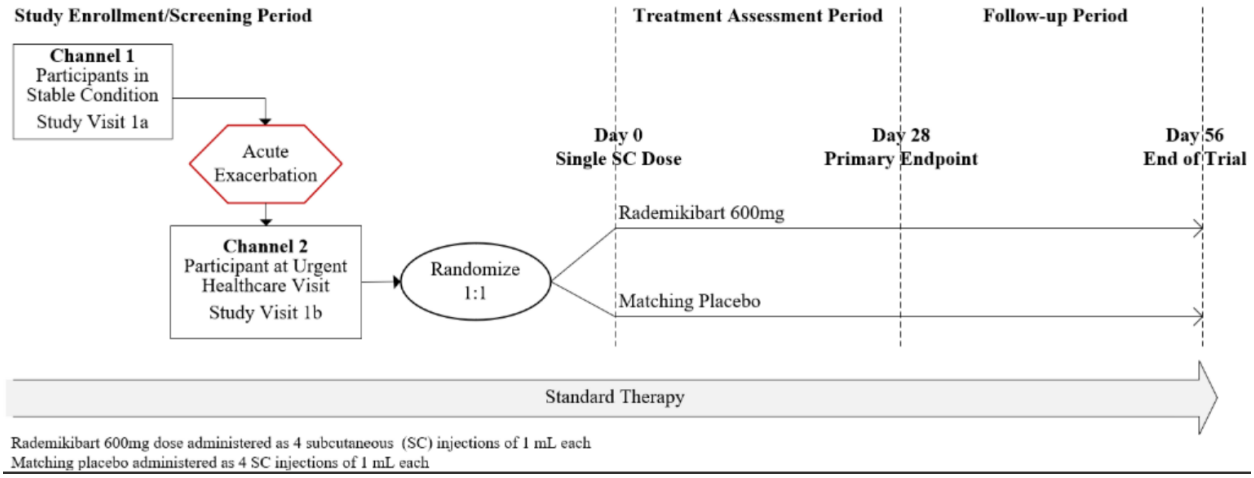
For participants who are hospitalized due to an acute COPD exacerbation at randomization (Day 0), inpatient or on-site follow-up will take place as outlined in the Schedule of Assessments (SoA; Table 5). On the day of discharge, FEV_1 measurements should be performed in the morning prior to discharge, including pre-BD and post-BD measurements.

For participants who are not hospitalized, on-site follow-up procedures will also follow the SoA (Table 5).

Hospitalized participants discharged from the hospital prior to Visit 3 and Visit 4, or participants that were not hospitalized for the index COPD exacerbation, have the option to consent to return to the trial site or have a home health care visit for spirometry assessments at Visit 3 and Visit 4.

One interim analysis (IA) is planned when approximately 80 participants have completed the Week 4 Visit (see Section 13.7), and the final analysis for the trial will be conducted after all participants have completed Week 8 or the End of Trial (EOT) Visit.

Figure 1: Trial Schema



6.2. Number of Participants

Approximately 160 adult participants with acute COPD exacerbation characterized by an eosinophilic phenotype will be randomized. The planned participant enrollment may be adjusted following the planned IA due to a sample size re-estimation.

6.3. Treatment Assignment

Participants will be randomized in a 1:1 ratio to 1 of the following double-blinded treatment groups, stratified by severity of the acute COPD exacerbation (requiring hospitalization or not [yes/no]) at baseline, and baseline smoking status [current or former]):

- **Rademikibart** 600 mg dose administered as 4 SC injections of 1 mL (150 mg) each.
- **Matching Placebo** administered as 4 SC injections of 1 mL each.

IP (rademikibart 600 mg SC or placebo SC) will be administered on Day 0 as per the SoA (Table 5).

6.4. Participant Duration

For participants who consent to participate in the trial while in a stable condition, the duration of the trial will be up to 34 weeks, which includes a Screening Period of up to 26 weeks, a 28-day Treatment Assessment Period, and a 28-day Follow-up Period.

For participants who consent to participate in the trial during the urgent healthcare visit for an acute COPD exacerbation, the duration of the trial will be approximately 8 weeks, which includes a Screening Period of up to 48 hours, a 28-day Treatment Assessment Period, and a 28-day Follow-up Period. A participant is considered to have completed the trial if they have completed all periods of the trial including the Follow-up Visit (Week 8). The end of the trial is defined as the date of the last visit of the last participant in the trial globally.

6.5. Dose Adjustment Criteria

Dose modification is not permitted.

6.5.1. Safety Criteria for Adjustment or Stopping Doses

Dosing for any individual participant will be stopped if the participant experiences a drug-related SAE or a drug-related significant nonserious AE which, in the opinion of the Investigator, physician, or Sponsor's medical representative, warrants discontinuation of the trial for that participant's well-being.

6.6. Criteria for Trial Termination

The Sponsor or designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the Sponsor.

Reasons for the early termination of the trial or early closure of a trial site by the Sponsor may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further IP development.
- New information has been obtained that negatively affects the risk-benefit assessment of the IP, including sufficient evidence indicating lack of efficacy or unacceptable safety concerns.
- Major defects are discovered in the trial design, making it difficult to evaluate the drug, or major deviations occur during the trial implementation that affect the overall evaluation of the IP.
- Sponsor decision.

Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected, and a trial-site closure visit has been performed.

The Investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

6.7. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) comprising members who are independent of the Sponsor and Investigators will be established for this trial. This committee will include externally based individuals with expertise in the diseases under trial, biostatistics, and/or clinical research.

The primary responsibilities of the DMC are to review and evaluate the safety data during the trial and review IA results. The DMC will also provide the Sponsor with appropriate recommendations on the conduct of the clinical trial to ensure the protection and safety of the participants enrolled in the trial. The DMC will also institute any measures that may be required for ensuring the integrity of the trial results during the trial execution. All activities and responsibilities of the DMC are described in the DMC charter.

The criteria for terminating the trial are provided in Section 6.6.

6.8. Independent Adjudication Committee

An Independent Adjudication Committee will be constituted to provide an independent, external, systematic and unbiased assessment of blinded data to confirm the diagnosis of Investigator reported non-fatal myocardial infarction, non-fatal stroke (hemorrhagic, ischemic, embolic), as well as cardiovascular deaths during the trials.

Adjudication Committee members' responsibilities and the process for data review are described in the Adjudication Committee Charter.

7. SELECTION AND WITHDRAWAL OF PARTICIPANTS

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Prospective participants may be screened and consented up to 26 weeks in advance of an acute exacerbation.

7.1. Inclusion Criteria

Participants are eligible to be included in the trial only if ALL of the following criteria apply:

1. Written informed consent obtained prior to performing any protocol-related procedures.
2. Adults (40 to 80 years, inclusive) at the time of signing the informed consent.
3. Body weight of ≥45 kg and body mass index within the range 16 to 35 kg/m^2 (inclusive) at Screening.
4. Physician-diagnosed COPD with duration of ≥12 months by medical chart or participant report; COPD is defined as dyspnea and/or chronic productive cough with current or historic evidence of spirometry confirming airflow obstruction (post-BD FEV_1/FVC ≤70%).
5. Must have experienced at least 1 COPD exacerbation requiring the use of systemic corticosteroids (oral or parenteral) within the previous 12 months prior to Screening.
6. Participants who consent to participate in the trial while in a stable condition must have a documented historical peripheral blood eosinophil count of ≥250 cells/μL within 12 months prior to Screening Visit 1a.
7. Current or former smoker with a history of smoking of ≥10 pack-years.

   Note: This includes tobacco, marijuana, and vaping products.
8. In the opinion of the Investigator, participant is willing and able to comply with all trial visits and trial-related procedures (such as, willing and able to perform entries of daily electronic diary [e-diary] patient-reported outcomes [PRO]s).
9. Women of childbearing potential, unless surgically sterile (including tubal ligation) and/or at least 2 years postmenopausal, should have a confirmed negative serum beta-human chorionic gonadotropin (β-hCG) test at Screening Visits 1a and/or 1b and agree to use a highly effective method of avoiding pregnancy from trial recruitment through Day 56, see Appendix B.

   Note: A female is considered of childbearing potential following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

Additional Inclusion Criteria for Current Acute COPD Exacerbation:

10. Current acute COPD exacerbation requiring an urgent healthcare visit for treatment.

Note: COPD acute exacerbation is defined as an acute increase in symptoms (1 or more of the following: cough frequency and severity, sputum production, dyspnea) beyond normal day-to-day variations leading to a change in medication.

For the purposes of this trial, an urgent healthcare setting may include an ED, a hospital inpatient ward, or an urgent healthcare facility equipped to provide the level of care specified in this protocol. The primary reason for ED visit, urgent healthcare visit, or hospitalization is for acute COPD exacerbation.

11. Peripheral blood eosinophil count of ≥300 cells/μL at Screening Visit 1b or as part of the assessment of the index acute COPD exacerbation within 72 hours prior to Screening Visit 1b.
12. Requires systemic corticosteroids as SoC treatment in the urgent healthcare setting for the current acute COPD exacerbation.

7.2. Exclusion Criteria

A participant who meets any of the following criteria will be ineligible to participate in this trial:

1. Previously received rademikibart; or a known systemic hypersensitivity or anaphylaxis to any biologic therapy, including any excipients.
2. Regular use of immunosuppressive medication (including but not limited to maintenance daily prednisolone, hydrocortisone, azathioprine, or weekly methotrexate) 12 weeks or 5 half-lives prior to randomization, whichever is longer.
3. Scheduled elective surgery or other procedures requiring general anesthesia during the trial.
4. Current diagnosis or a history of asthma, according to the Global Initiative for Asthma; or participants with a current diagnosis or history of Asthma COPD Overlap Syndrome.
5. Other respiratory disorders: A diagnosis of alpha-1 antitrypsin deficiency as the underlying cause of COPD, lung cancer, clinically overt bronchiectasis (*Note: focal fibrotic pulmonary lesions are not exclusionary*), primary pulmonary hypertension, interstitial lung diseases, or any other respiratory condition that might, in the opinion of the Investigator, compromise the safety of the participant or affect the interpretation of the results.
6. Unstable ischemic heart disease, cardiomyopathy, heart failure (New York Heart Association Class III or IV), uncontrolled hypertension which, in the Investigator's judgement, may put the participant at risk or negatively affect the outcome of the trial. Cardiac arrhythmias including paroxysmal (eg, intermittent) atrial fibrillation are excluded. Participants with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (ie, selective beta blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) and stable appropriate level of anticoagulation for at least 6 months may be considered for inclusion.
7. Transient ischemic attack or stroke <6 months from Screening Visit; hospitalization for any cardiovascular or cerebrovascular event <6 months from Screening Visit.

Note: this criterion should be confirmed at both Screening Visit 1a and Visit 1b.

8. Participants with a history of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, ophthalmologic, respiratory, gastrointestinal, cerebrovascular, substance and/or alcohol abuse, or other significant medical illness or disorder which, in the Investigator's judgement, could interfere with the trial or require treatment that might interfere with the trial. Specific examples include but are not limited to poorly controlled diabetes.
9. Another clinically significant pulmonary or systemic disease associated with an elevated peripheral blood eosinophil count (eg, allergic bronchopulmonary aspergillosis, eosinophilic granulomatosis with polyangiitis, hyper-eosinophilic syndrome, and helminth infection).
10. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis), despite infection resolution; or unusually frequent, recurrent or prolonged infections, in the opinion of the Investigator.
11. History of known immunodeficiency disorder (including human immunodeficiency virus [HIV]-1 or HIV-2).
12. Known medical history of hepatitis B or C.
13. History of alcohol abuse and/or drug abuse within 12 months prior to Screening Visit 1a and/or 1b.
14. History of cancer except basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy >1 year prior to entry or other malignancies treated with apparent success with curative therapy >5 years prior to entry.
15. Having undergone lung volume reduction surgery or lung resection for any other reason, eg, lung carcinoma.
16. Chronic treatment with long-term oxygen therapy (LTOT) or nocturnal oxygen therapy required for >15 hours a day. Oxygen pro re nata (PRN) use (ie, ≤15 hours per day) is not exclusionary. Oxygen use during an exacerbation is permitted.
17. Participants on long-term macrolide (eg, azithromycin) therapy, unless on stable therapy for >12 months, with the exception of prior treatment for an acute COPD exacerbation.

Additional Exclusion Criteria for Current Acute COPD Exacerbation:

18. Fever recorded as >38°C measured using the tympanic temperature and/or a suspected pulmonary infection (chest radiograph demonstrating consolidation).
19. Any condition (ie, respiratory failure necessitating non-invasive or invasive ventilation, or impending hemodynamic compromise, or impending intensive care unit [ICU] admission) that, in the opinion of the Investigator, would interfere with evaluation of the IP or interpretation of trial results.
20. Current acute COPD exacerbation for which SoC was started >48 hours prior to Screening Visit 1b.

21. Chest X-ray or computed tomography (CT) scan at Screening Visit 1b reveals evidence of clinically significant abnormalities not believed to be due to the presence of COPD, or a clinically significant pulmonary infection (chest radiograph demonstrating consolidation) identified by chest X-ray (CT scan) at Screening Visit 1b.
22. Participants with a prolonged QTc interval (male >450 msec, female >470 msec, Fridericia correction); any other clinically significant abnormalities in electrocardiogram (ECG) at Screening, in the opinion of the Investigator.
23. An alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥2.5 × the upper limit of normal (ULN) and/or bilirubin level ≥1.5 × ULN at Screening Visit 1b.
24. Any other acute illness other than the acute COPD exacerbation at the start of the trial at Visit 1b.
25. Any clinically significant abnormal findings in physical examination, vital signs, hematology, clinical chemistry or urinalysis which, in the opinion of the Investigator, may put the participant at risk because of their participation, or may influence the results of the trial or their ability to complete the duration of the trial.
26. Female participant who is pregnant, lactating or breast-feeding, or has a positive urinary β-hCG test prior to randomization.
27. Evidence of clinically significant non-respiratory active infection, including ongoing chronic infection.
28. Receipt of any marketed nonbiologic drug that modulates type 2 cytokines (eg, suplatast tosilate) 30 days or 5 half-lives prior to randomization, whichever is longer.
29. Receipt of any marketed (eg, dupilumab or other monoclonal antibody) or any investigational biologic for COPD or other diseases within 16 weeks or 5 half-lives prior to randomization, whichever is longer.
30. Live, attenuated vaccinations within 4 weeks prior to randomization or planned live, attenuated vaccinations during the trial.
31. Treatment with oral corticosteroids and/or hospitalization for an exacerbation of COPD (not for the index acute COPD exacerbation) completed less than 4 weeks prior to randomization.
32. Donation of blood, plasma or platelets within 90 days prior to randomization.
33. Receipt of intravenous immunoglobulin or blood products within 30 days before randomization into the trial.
34. Receipt of any investigational nonbiologic drug within 30 days or 5 half-lives prior to randomization, whichever is longer.

7.3. Lifestyle Considerations

7.3.1. Meals and Dietary Restrictions

Participants should avoid eating a large meal for at least 2 hours prior to all spirometry assessments at the center.

Participants should not eat or drink for at least 1 hour prior to having the fractional exhaled nitric oxide (FeNO) assessment.

7.3.2. Caffeine, Alcohol, Tobacco, and Other Habits

Participants with a history of alcohol or drug abuse within 12 months of screening are excluded from the trial. Chronic alcohol or drug abuse is restricted throughout the conduct of the trial.

Participants will:

- Refrain from smoking (including cigarettes [including electronic cigarettes/pipes, vaporizers, cigars, pipes) for at least 1 hour prior to and during the spirometry and FeNO assessments.
- Refrain from drinking beverages with high levels of caffeine, such as tea and coffee, for at least 2 hours prior to each spirometry assessments.

7.3.3. Physical Activity

Participants will abstain from strenuous exercise for ≥2 hours prior to spirometry assessments.

7.3.4. Other Activity

Participants must be willing to visit the clinic per the SoA (Table 5).

Participants should not donate blood or plasma from the time they are enrolled in the trial, ie, signing the ICF, until 8 weeks following the dose administration of IP.

7.4. Screen Failures

Screen failures are defined as participants who signed the ICF to participate in the clinical trial but are not subsequently randomized. These participants are not required to complete the EOT visit assessments. Screen failures should be recorded in the Interactive Response Technology (IRT) according to instructions in the IRT manual. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Given the variable nature of COPD exacerbations, participants who initially are screen failures for the trial solely due to the ineligible eosinophil count (ie, eosinophil count of <300 cells/µL) at Screening Visit 1b, are allowed to re-screen no more than twice if they experience another COPD exacerbation, provided it is deemed appropriate by the Principal Investigator. If the reason for Screen Failure was transient (eg, a recent COPD exacerbation within 4 weeks prior to Screening, ineligible medication/vaccine washout at Screening, or clinically significant pneumonia identified by chest X-ray [CT scan] at Screening), participants may potentially be considered for re-screening; however, the maximum combined number of chest X-rays and/or CT scans must not exceed 2 for screening. These cases should be discussed with the Sponsor Medical Monitor/designee and documented in the Investigator Study File.

If re-screened, the participant should be assigned a new participant number. The participant must meet all eligibility criteria at the time of re-screening to qualify for the trial.

7.5. Discontinuation of IP

If a participant is discontinued from IP, the participant will be asked to continue attending trial visits to the EOT Visit (Week 8).

7.5.1. Criteria for Permanent Discontinuation of IP

Participants should be discontinued from IP in the event of:

1. The participant withdraws his/her consent to participate in the trial.
2. Anaphylactic reaction or other severe hypersensitivity reaction attributed to IP administration.
3. AE, laboratory abnormality, or inter-current illness which, in the opinion of the Investigator, indicates that continued treatment and/or participation in the trial is not in the best interest of the participant
4. Evidence of pregnancy.
5. Participant is significantly non-compliant with trial procedures which would put the participant at risk for continued participation in the trial in consultation with the Sponsor Medical Monitor or designee.
6. Important protocol deviation or requirement for medication or procedure prohibited by the protocol.
7. Severe laboratory abnormalities (Appendix C):
    a. AST and/or ALT ≥3 × ULN in combination with total bilirubin ≥2 × ULN and no other explanation other than IP can be determined.
    b. Confirmed AST and/or ALT >5 × ULN (for more than 2 weeks).

7.5.2. Temporary Discontinuation or Interruption of IP

Temporary discontinuation or interruption of IP is not applicable for this single-dose trial.

7.5.3. Rechallenge

Rechallenge is not allowed.

7.6. Participant Withdrawal from the Trial

The Investigator will make reasonable efforts to keep each randomized participant in the trial. However, participation in the trial is strictly voluntary. A participant has the right to withdraw from the trial at any time for any reason, without any reprisal.

Randomized participants who are terminated early from the trial will have an EOT Visit conducted as soon as possible as per the SoA (Table 5). All information, including the reason for early withdrawal, will be recorded in the participant's trial records and in the eCRF.

If the participant refuses to complete EOT/Follow-up Visit procedures or continued data collection, this will be documented.

Any participant who consents to the trial as a stable participant and is not randomized to receive IP is considered a screen failure (see Section 7.4). These participants are not required to complete the EOT Visit assessments. This includes participants who did not have an acute exacerbation prior to the close of enrollment in the trial and prior to them reaching Visit 1b.

7.7. Lost to Follow-Up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and if the trial site is not able to get in contact with the participant.

The following actions must be taken if a participant fails to return to the clinic for a required trial visit:

- The trial site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the trial.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 2 attempts of contact by telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the trial.

8. TREATMENT OF PARTICIPANTS

8.1. Description of Investigational Product

Rademikibart drug product is provided as a colorless-to-pale yellow sterile solution at 150 mg/mL concentration in a 1 mL single-use PFS that delivers 1.0 mL solution.

Placebo for rademikibart is provided as colorless-to-pale yellow sterile solution containing the same excipients as the rademikibart drug product in a 1 mL single-use PFS that delivers 1.0 mL solution.

The IP will be administered by SC injection (see Section 9.4).

8.2. Concomitant Medications

All medications taken from 3 months prior to the participant's initial Screening Visit 1a or Visit 1b through the end of the trial, including those given in the urgent healthcare setting to treat the index acute COPD exacerbation, should be recorded in the participant's source document and in the eCRF.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at Screening Visits 1a and/or 1b or receives following Screening and throughout the trial must be recorded in the source documents and eCRF along with:

- Reason for use.
- Start and end date of administration.
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding prior or concomitant medication or procedures.

8.2.1. Prohibited Concomitant Therapy

The concomitant treatments are not permitted during the Screening Period or the randomized Treatment Assessment Period are listed in Table 3.

Table 3: Prohibited Therapy

Prohibited Medication/Therapy:	**Usage:**
Rescue medications other than salbutamol/albuterol or levosalbutamol/levalbuterol (for example, short-acting anticholinergics [eg, ipratropium bromide])	Not recommended during the trial period. In case of use in exceptional circumstances (eg, prescribed by a physician not participating in the trial or used for managing an COPD exacerbation event), their use will be documented in the participant's file and reported in the eCRF. Short-acting anticholinergics (eg, ipratropium bromide) for use as a rescue medication are not permitted from the Screening Visit 1b through

	completion of the trial, unless required for treatment of an acute COPD exacerbation.
Any marketed nonbiologic drug that modulates type 2 cytokines (eg, suplatast tosilate)	Not allowed 30 days or 5 half-lives (whichever is longer) prior to randomization, and throughout the trial.
Any marketed biologic (eg, dupilumab, or other monoclonal antibody) or investigational biologic treatment (including investigational use of an approved biologic)	Not allowed 16 weeks or 5 half-lives (whichever is longer) prior to randomization, throughout the trial until the Follow-up Visit Week 8.
Any investigational nonbiological drug or treatment (including investigational use of an approved drug)	Not allowed 30 days prior or 5 half-lives (whichever is longer) to randomization, and throughout the trial.
Live attenuated vaccines (see Appendix I)	Not allowed 4 weeks prior to randomization, and during the trial including the Follow-up Period.
Any immunomodulators or immunosuppressives (except for short term usage of oral corticosteroids for COPD exacerbation)	Not allowed 12 weeks or at least 5 half-lives (whichever is longer) prior to randomization, and throughout the trial.
PDE4 inhibitors (roflumilast)	Use of PDE4 inhibitors (eg, roflumilast) from Screening throughout the trial, unless on stable therapy for >12 months prior to Screening Visit.
Macrolide antibiotics (eg, azithromycin)	Not allowed for chronic use from Screening throughout the trial, unless on stable therapy for >12 months, with the exception of prior treatment for a COPD exacerbation. If treatment duration is expected to exceed 14 days, the Sponsor Medical Monitor must be contacted.
Intravenous immunoglobulin therapy or blood products	Not allowed 30 days prior to randomization, and throughout the trial.

COPD = chronic obstructive pulmonary disease; eCRF = electronic case report form; PDE = phosphodiesterase.

8.2.2. Permitted Concomitant Therapy

8.2.2.1. COPD Medications and Non-Drug Therapies

To be eligible to be randomized in this trial, participants must present with an acute COPD exacerbation characterized by an eosinophilic phenotype and required systemic corticosteroids as

SoC treatment in the urgent healthcare setting for the acute exacerbation. SoC for the index acute exacerbation is defined for this protocol as treatment with oral/systemic corticosteroid[s] (40 mg/day prednisone or equivalent) for 5 days with or without antibiotic(s) for 7 days; the modification of the dose and/or duration of prednisone (40 mg/day or equivalent) and/or the antibiotic is not recommended but may be allowed according to the Investigator's/medically qualified designee's judgement.

The start of SoC is defined as the start of either oral or systemic corticosteroids(s) or antibiotic(s), whichever is earliest.

Note: SoC must be documented in the participant's source documentation and in the eCRF. The use of other medications for treatment of the index acute COPD exacerbation and any subsequent COPD exacerbation(s), if applicable, is at the discretion of the Investigator or medically qualified health care personnel. Use of medication for treatment of subsequent exacerbations does not need to follow the SoC requirements for the index acute exacerbation.

In addition, participants are instructed to continue their regular COPD maintenance treatments (eg, LAMAs, LABA/ICS combinations, LABA/LAMA combinations, or LABA/LAMA/ICS combinations) for the duration of the trial. However, participants must withhold the morning dose of usual scheduled COPD medications on the morning of the spirometry assessments, except when treatment is needed for an acute COPD exacerbation.

Note: Modification(s) of the dosing regimen for the regular COPD maintenance treatments is(are) permitted as deemed medically appropriate by the Investigator/medically qualified designee; the modifications will be recorded in source documents and eCRF.

Other concomitant COPD maintenance medications may be allowed at the discretion of the Investigator following consultation with the Sponsor Medical Monitor, with the exception of short-acting anticholinergics for use as rescue medication.

Oxygen for intermittent use or PRN therapy ≤15 hours per day is allowed. LTOT or nocturnal oxygen therapy required for >15 hours is excluded throughout the trial.

8.2.2.2. Non-COPD Medications and Non-Drug Therapies

All medications for other disorders are permitted (except those listed in Table 3) as long as the dose remains constant whenever possible, and their use would not be expected to affect the efficacy (especially lung function) or safety assessments. The use of a continuous positive airway pressure (CPAP) device is permitted during the trial, provided that this therapy was initiated prior to Screening and the participant is on a stable regimen. Participants that require acute use of CPAP cannot be enrolled. Use of this therapy is to be recorded in the source document and eCRF. Participation in the acute or maintenance phase of a Pulmonary Rehabilitation Program during the trial is permitted. Participation is to be recorded in the source document and eCRF.

8.2.2.3. Rescue Therapy

The trial site will supply each randomized participant with albuterol [salbutamol] metered dose inhaler (MDI) for use in performing the post-BD FEV_1 assessments and as rescue medication for use as needed throughout the trial for treatment of acute symptoms of COPD.

A participant may use a different short-acting β-agonist (SABA) inhaler other than that provided (eg, a different brand of albuterol/salbutamol/ levalbuterol that is distributed at Screening). All SABA inhaler dosing (puffs) must be recorded in the daily e-diary.

In addition, rescue use of albuterol (salbutamol) nebules administered via nebulization is discouraged, except as urgent treatment during a COPD exacerbation. Occasions where SABA is administered via nebulization will be recorded separately from metered dose inhaler inhalations in the e-diary. Use of low dose ICS-formoterol as rescue medication is not allowed during the trial.

Although the use of rescue albuterol (salbutamol) medications is allowable at any time during the trial, its use should be delayed for at least 4 hours prior to completing the pre-BD spirometry assessments, unless required for treatment of an acute exacerbation COPD. It is anticipated that participants who are randomized into the trial will receive albuterol as part of the routine treatment of the acute COPD exacerbation during Visit 1b and Visit 2. In this instance spirometry should be scheduled to coincide with this treatment to allow post-BD recordings to be measured.

8.3. Treatment Compliance

The date and time of the dose administered to the participant will be recorded in the source documents. The dose of IP and trial participant identification will be confirmed at the time of dosing by a member of the trial site staff other than the person administering the IP.

8.4. Randomization and Blinding

8.4.1. Participant Assignment

At Screening (Visit 1a or 1b), all participants are assigned a unique sequential identification (ID) number by site personnel. The participant number is a 7-digit number consisting of a 2-digit country code, a 2-digit site identifier, and a sequential 3-digit participant number.

Following the Screening Period, eligible participants will be randomized to one of the 2 treatment arms.

8.4.2. Randomization

All participants meeting enrollment criteria will be randomized at baseline (Day 0) to receive treatment with either rademikibart 600 mg SC or volume-matched placebo.

As participants qualify for randomization, they will be assigned to treatment by the IRT System. The random treatment assignments will be done in a 1:1 ratio. Randomization will be stratified by stratified by severity of the index acute COPD exacerbation (requiring hospitalization or not [yes/no]) at Baseline, and smoking status at Screening (current or former).

See Section 7.4 for details on screen failures.

8.4.3. Blinding and Unblinding

This is a double-blind trial; neither the participants nor the Investigator will be aware of the treatment assignment for the participants. Blinding will be maintained throughout the trial by the use of active and placebo treatment of similar appearance and volume-matched dosing.

All Sponsor staff or designee will remain blinded to the treatment allocation until after the trial database is locked with the following exceptions:

- The independent statistician preparing the randomization codes, providing data to the DMC, and conducting the unblinded IA.
- A limited number of the Sponsor's senior management team (independent of the clinical trial team) who will receive results from the IA.
- The staff of the Sponsor or designee responsible for packaging IP.
- The staff of the Sponsor or pharmacovigilance vendor responsible for assessment and reporting of a suspected unexpected serious adverse reaction (SUSAR).
- The staff of contract research organizations (CROs) involved in processing the PK samples.
- The quality assurance auditors, where necessary.

8.4.4. Emergency Unblinding

The IRT interactive web response system will provide access to unblinded participant treatment information in the case of a medical emergency. In case of emergency when the treatment information is required by the Investigator to ensure a participant's safety in managing a medical condition, the treatment may be unblinded at the site by using a code break module. Whenever possible, the Investigator should contact the Sponsor prior to unblinding.

In the case of any intentional or accidental unblinding, the Sponsor or designee must be notified immediately. Whenever a treatment sequence is prematurely unblinded, the reason, date and time of the unblinding, and the individual who broke the blind, must be documented.

9. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

9.1. Investigational Product

The rademikibart drug product is formulated as a liquid sterile solution at 150 mg/mL in 10 mM L histidine, 60 mM trehalose, and 100 mM NaCl with 0.02% polysorbate 80 at pH 6.2. It is provided as a colorless-to-pale yellow sterile solution at 150 mg/mL concentration in a 1 mL single-use PFS that delivers 1.0 mL solution.

Placebo solution is identical in appearance and content to the active solution except for rademikibart.

All IPs (rademikibart and placebo) will be supplied as a sterile PFS with a pre-assembled needle safety device. Each PFS is intended for a single 1 mL dose (150 mg) administered subcutaneously.

The individual IP information is presented in Table 4.

Table 4: Investigational Products

Intervention Name	**Rademikibart**	**Placebo**
Intervention Description	Novel anti IL-4Rα human monoclonal antibody	Matched-volume placebo
Formulation	Injection	Injection
Unit Dose Strength(s)	150 mg in 1 mL	Matching volume
Dosage	600 mg (4mL) 4 injections	Matching volume 4 injections
Duration of Treatment	Single dose administration	Single dose administration
Route of Administration	Subcutaneous injection	Subcutaneous injection

9.2. Investigational Product Packaging and Labeling

The PFSs of IP are packaged in paper boxes with supportive custom inserts.

Clinical labeling and packaging for all studies are conducted under Good Manufacturing Practice (GMP) manufacturing conditions. Labels are printed in accordance with local law with approved label specifications and are 100% visually inspected by Quality Assurance. Blinding of kit contents is maintained by assigning kit numbers to each package which are printed on both the drug product and the package labels. Kit numbers are assigned according to a pre-defined randomization schedule which is maintained within an IRT system.

9.3. Investigational Product Storage

The rademikibart drug product and matching placebo solution are to be stored between 2°C to 8°C. The drug product is stable for at least 1 month at 30°C.

9.4. Investigational Product Preparation and Administration

Rademikibart is intended for SC administration. The trial is designed to evaluate the efficacy and safety of a single 600 mg SC dose of rademikibart (administered as 4 separate 150 mg injections) as adjunct therapy to standard therapy.

IP will be administered by a qualified healthcare professional (eg, physician, physician assistant, nurse practitioner, pharmacist or trial nurse) at the site. The anatomical location of the injection site must be recorded in the source documents and in the eCRF.

The person administering the dose will wipe the skin surface of the upper arm, anterior thigh, or abdomen with alcohol and allow to air dry. The skin will be pinched to isolate the SC tissue from the muscle. The needle will be inserted at a 45-degree angle approximately halfway into the SC tissue. The trial medication will be slowly injected (at least 5 second duration is recommended) into the SC tissue using gentle pressure. The area should not be massaged after injection.

As multiple injections are required for IP administration, each injection site should be separated by at least 3 cm. Administration of the dose will be recorded in eCRF.

In the case of any incorrect administration of IRT-assigned treatment, the Sponsor must be notified immediately (within 24 hours) after first knowledge. Further details on IP administration is provided in the Pharmacy Manual.

9.5. Investigational Product Accountability

The Investigator (or designee) is responsible for maintaining accurate accountability records of the IP throughout the clinical trial. Appropriately trained personnel will inventory the IPs received and will maintain records of disposition of the drugs, including dates, quantity, and use. The Investigator or designee must maintain adequate records of the IPs (ie, accountability or dispensing logs) throughout the clinical trial: distribution, including the date received, number and units received, and lot numbers, storage, dispensing, and return or destruction of all IP. All dispensing and accountability records will be available for Sponsor or designee review. IP accountability records will be reviewed and verified during on-site and remote monitoring visits. At the end of the trial, the Sponsor or designee will conduct a final reconciliation of all IP accountability records.

9.6. Investigational Product Handling and Disposal

Further guidance and information for the final disposition of unused IP is provided in the Pharmacy Manual.

10. ASSESSMENT OF EFFICACY

Efficacy will be assessed via evaluations of the treatment failure rate, subsequent acute COPD exacerbations, spirometry assessments, venous blood gas (VBG) analysis (only for the hospitalized participants), patient-reported outcomes (PROs), and healthcare resource utilization and economics per the SoA (Table 5). PRO assessments carried out at trial visits will be completed as the first assessment in the visit schedule before spirometry or any other trial procedure.

10.1. Treatment Failure

Treatment failure is defined as death due to any cause, (re)admission to a hospital for COPD, ED (re)visit or unscheduled medical visit for worsening of COPD symptoms, or the necessity to intensify pharmacologic treatment (including second course of systemic steroids for COPD exacerbation) within 28 days after randomization.

10.2. Acute Exacerbation

COPD exacerbation data will be collected through Trial Day 56. For the purpose of this trial, COPD exacerbation is defined by protocol as either:

- Clinically significant worsening of COPD symptoms, including increases in dyspnea, wheezing, cough, sputum volume, and/or increase in sputum purulence.
- Exacerbation severity is further defined as moderate if treatment with systemic corticosteroids and/or antibiotics was required, or severe if they resulted in hospitalization or observation for over 24 hours in an ED or urgent healthcare facility.

All other exacerbations will be classified as “mild.”

For both moderate and severe events to be counted as separate events, they must be separated by at least 14 days.

The following information will be collected for each COPD exacerbation:

- Date of onset.
- Date of visit to healthcare provider or ED.
- Treatment.
- Resolution date.

10.3. Spirometry

Spirometry will be performed according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (Miller et al. 2005; Graham et al. 2019) at the timepoints specified in the SoA (Table 5). Spirometry assessments, including FEV_1, and FVC (both the absolute measurement and the percentage of predicted normal value will be recorded), should be made as close to the scheduled timepoints as possible. In addition, protocol-specified clinic spirometry must be completed in accordance with the lifestyle restrictions as defined in Section 7.3.

Spirometry will be performed preferably in the morning; afternoon is allowable in the exceptional circumstance when morning spirometry cannot be performed. Current smokers need to be reminded not to smoke for at least 1 hour before spirometry. For each participant, the same spirometer and standard spirometric techniques, including calibration, will be used to perform spirometry at all visits and, whenever possible, the same person should perform the measurements.

Baseline FEV_1 is defined as the post-BD FEV_1 performed at Visit 2 before IP administration.

At the timepoints SoA (Table 5), if the participant's condition allows, post-BD FEV_1 will be conducted approximately 15 to 30 minutes after the participant-administers 4 inhalations of albuterol (salbutamol) via MDI (ie, total of 400 mcg) using a spacer device.

It is anticipated that participants who are randomized into the trial will receive albuterol (salbutamol) as part of the routine treatment of the acute COPD exacerbation during Visit 2. In this case, spirometry should be scheduled to coincide with this treatment to allow post-BD recordings to be measured.

For hospitalized participants, post-BD spirometry should also be performed at the timepoints specified in the SoA (Table 5), including V3 and V4, provided the participant's condition allows.

Hospitalized participants discharged from the hospital prior to Visit 3 and Visit 4, or participants that were not hospitalized for the index COPD exacerbation, have the option to consent to return to the trial site or have a home health care visit for spirometry assessments at Visit 3 and Visit 4.

If the participant can tolerate BD washout, at Visit 6, Visit 8, Visit 9, and on the day of discharge (only for hospitalized participants), spirometry will be performed prior to administering maintenance COPD medication(s) (pre-BD) and post-BD (as defined above). Participants should withhold their usual maintenance therapies on the day(s) when pre-BD spirometry is being performed as below:

- Withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours,
- Withholding the last dose of LABA for at least 12 hours [ultra-long-acting LABA like vilanterol should be withheld for at least 24 hours]
- Withholding the last dose of ipratropium bromide for at least 8 hours
- Withholding the last dose of LAMA for at least 24 hours

This washout period will be verified before performing the measurements. After completing the pre-BD spirometry, the post-BD spirometry should follow the steps as that at V2 before IP administration.

Where multiple assessments are scheduled at the same time point, the sequence of assessments should ideally be as shown below. However, during the Screening Visit (Visit 1b) and/or the Randomization Visit (Visit 2), this order may be modified as needed, including instances where some or all of these procedures are performed as part of routine/urgent/ inpatient hospitalized care.

- PROs and other questionnaires.
- Vital signs.

- 12-lead ECG.
- FeNO.
- Spirometry assessment (pre-bronchodilator).
- Post-bronchodilator spirometry.
- e-diary download.
- Blood sampling and laboratory assessments.
- IP administration (only applicable to Visit 2).

Further details on spirometry will be available in a separate operational manual provided to the sites.

10.4. VBG Analysis (for Hospitalized Participants Only)

VBG will only be assessed in hospitalized participants. VBG analysis will be as outlined in the SoA (Table 5) and measurements will include pH, partial pressure of oxygen, partial pressure of carbon dioxide, oxygen saturation, and the bicarbonate (HCO_3^-)concentration.

10.5. Patient-reported Outcome Questionnaires

Patient reported outcomes (PRO) data will be captured electronically using a handheld device at home and at the site. Site personnel will be trained on the use of the device and detailed procedures for using the device will be described in a separate instruction manual.

Participants will be trained on home use of the e-diary at Visit 1b and throughout the trial on an as needed basis. Training will emphasize the importance of completing the PRO assessments as scheduled to capture the participant's experience and meet the objectives of the trial.

The participant will complete the following assessments daily via the e-diary at the timepoints defined per the SoA to:

- Respond to the COPD exacerbation and symptom scale questions of the Exacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT)-PRO tool every evening (typically at bedtime).
- Respond to Dyspnea Numerical Rating Scale (NRS) twice daily.
- Record use of short-acting rescue medications twice daily.

Investigator/authorized delegate will check participant’s adherence to the PRO assessment schedule as is necessary and at each trial visit to minimize missing data.

The other questionnaires, the COPD Assessment Test (CAT) (see Section 10.5.1) and the St. George's Respiratory Questionnaire (SGRQ) (see Section 10.5.2), will only be administered at on-site visits or telephone call visit as outlined in the SoA (Table 5). Participants responses to the questionnaires will be captured electronically using a handheld device at the site with the exception of using paper CAT questionnaires at the telephone call visit (Visit 7). Electronic upload of a participant completed paper questionnaire is permitted when use of the electronic questionnaire is not possible.

For participants who are hospitalized, if a participant is too ill to complete the PRO questionnaires without assistance on a given day, a member of the trial staff may verbally recite the questions verbatim to the participant and the staff member may enter the participant's verbal response in the e-diary. The participant's confirmation of the accuracy of the staff member's transcription will be documented in the source document/e-diary. As the PROs are validated for self-administration only, the reason for this deviation will also be recorded. Hospitalized participants will be encouraged to complete the e-diary personally as soon as possible and will be trained to do so before discharge.

PRO questionnaires should be completed prior to any other assessments or procedures per visit. Participants should complete the CAT at relevant trial visits per the SoA prior to performing any other trial procedures (including concurrent medication assessment, AE assessment, clinic spirometry, etc.), and prior to completion of the SGRQ. However, during the Screening Visit (Visit 1b) and/or the Randomization Visit (Visit 2), this order may be modified as needed, including instances where some or all of these procedures are performed as part of routine/urgent/inpatient hospitalized care.

10.5.1. COPD Assessment Test

COPD-related health status will be assessed using the COPD Assessment Test (CAT) (Jones et al. 2009; Jones et al. 2012); see Appendix G. The CAT (www.CATestonline.org) is a validated, short and simple patient-completed questionnaire, which has been developed for use in routine clinical practice to measure the health status of patients with COPD. The CAT is designed to measure overall COPD-related health status for the assessment and long-term follow-up of individual patients. The CAT is an 8-item questionnaire suitable for completion by all patients diagnosed with COPD. When completing the questionnaire, participants rate their experience on a 6-point scale, ranging from 0 (no impairment) to 5 (maximum impairment) with a scoring range of 0 to 40 (Jones et al. 2009; Jones et al. 2012).

10.5.2. St. George's Respiratory Questionnaire

The St. George's Respiratory Questionnaire is a 50-item questionnaire designed to measure and quantify health status in adult patients with chronic airflow limitation; see Appendix F (Jones et al. 1991; Jones et al. 1992). A global score ranges from 0 to 100. Scores by dimension are calculated for 3 domains: Symptoms, Activity and Impacts (Psycho-social) as well as a total score. Lower score indicates better quality of life.

The first part ("Symptoms") evaluates symptomatology, including frequency and severity of cough, sputum production, wheeze, breathlessness and the duration and frequency of attacks of breathlessness or wheeze. The second part has 2 components: "Activity" and "Impacts".
The "Activity" section addresses disturbances to a participant's daily physical activities.
The "Impacts" section covers a range of effects that chest troubles may have on a participant's daily life and psycho-social functions (eg, daily life activities and functioning, employment, physical functioning, emotional impact, stigmatization, and a participant's perceptions when treated). The recall period of the questionnaire is over the past 4 weeks.

Psychometric testing has demonstrated its repeatability, reliability and validity. Sensitivity has been demonstrated in clinical trials. A minimum change in score of 4 units was established as

clinically relevant after patient and clinician testing. The SGRQ has been used in a range of disease groups including asthma, COPD, and bronchiectasis.

10.5.3. Dyspnea Numerical Rating Scale

Daily dyspnea intensity will be evaluated by having the participant respond to the question "How much shortness of breath you are having right now?" twice a day (within 30 minutes of waking up [morning] and going to bed [evening], while they are resting) in e-diary with a 0 to10 NRS; see Appendix E. Participants will be asked to rate their shortness of breath by circling a number from 0 to 10, with 0 being no shortness of breath and 10 being shortness of breath as bad as it can be.

The Rome Proposal of COPD exacerbation reached a consensus to recommend the visual analog scale to quantify the severity of the resting dyspnea in patients with COPD (Celli et al. 2021), which has been validated against ventilatory loads (Gift and Narsavage 1998), can be represented by a numerical scale from 0 to 10 (Gift and Narsavage 1998), and has a minimally clinical important difference of 1 (Ekstrom et al. 2020). The NRS is a valid measure of present dyspnea in COPD patients which was supported by the high correlation of its scores with scores from the Dyspnea Visual Analog Scale.

10.5.4. Exacerbations of Chronic Pulmonary Disease Tool

Exacerbations of Chronic Pulmonary Disease Tool – Patient-Reported Outcome (EXACT-PRO) is a PRO instrument designed to capture information on the occurrence, frequency, severity, and duration of exacerbations of disease in patients with COPD (Leidy et al. 2011; Leidy et al. 2014). EXACT-PRO captures information on the severity of the respiratory and systemic manifestations of a COPD exacerbation as reported by the patient (Leidy et al. 2011). Development and validation history of the tool is consistent with guidelines proposed by the FDA, European Medicines Agency (EMA), and well-known measurement principles.

The instrument is a daily diary composed of a total of 14 items representing the following domains:

- Breathlessness (5 items),
- Cough and sputum (2 items),
- Chest symptoms (3 items),
- Difficulty bringing up sputum (1 item),
- Tired or weak (1 item),
- Sleep disturbance (1 item), and
- Scared or worried (1 item).

The instrument is to be completed every evening (typically at bedtime) using an e-diary. However, at Visit 2 (Randomization) only, the EXACT-PRO is to be completed as the first assessment before randomization and hence can be completed in the morning or afternoon. The daily recording of information allows an assessment of the underlying day-to-day variability of a participant's symptoms and facilitates the detection of symptom worsening indicative of a COPD

exacerbation. The total score for EXACT-PRO ranges from 0 to 100. The EXACT total score assesses COPD exacerbations. The higher the score, the more severe are the symptoms.

The Evaluating Respiratory Symptoms in COPD (E-RS: COPD) consists of 11 items from the 14-item EXACT-PRO instrument. E-RS: COPD is intended to capture information related to the respiratory symptoms of COPD (ie, breathlessness, cough, sputum production, chest congestion, and chest tightness). The E-RS has a scoring range of 0 to 40 (Leidy et al. 2014). Three subscales of the E-RS: COPD are used to describe different symptoms; dyspnea, cough and sputum and chest symptoms.

In addition to the collection of EXACT-PRO, participants will also complete daily e-diary questions to provide information on other symptoms suggestive of exacerbation, such as sputum purulence (color), wheezing, sore throat, colds (nasal discharge and/or nasal congestion), and fever without other cause.

10.5.5. Rescue Medication Use

Use of rescue medication (albuterol [salbutamol]) including inhaler and nebulizer use will be captured twice daily in the e-diary.

Inhaler usage will be reported as the number of puffs (ie, the sum of different relievers, if applicable) in a given period whereas nebulizer use will be reported as the number of times.

Rescue medication usage at night will be assessed in the morning and rescue medication used during the day will be assessed in the evening. For participants who are hospitalized and/or if the participant is too ill to complete the e-diary on his/her own on a given day, a member of the trial staff may enter the participant's use of non-nebulized rescue medication and/or the number of nebulized treatments over the given period in the e-diary, as applicable. The participant's confirmation of the accuracy of the staff member's transcription will also be documented in the e-diary/source document.

10.6. Healthcare Resource Utilization and Economics

A questionnaire of health care resource utilization (physician visit, hospitalization, ICU admission, emergency or urgent medical care facility visit) will be collected by the Investigator for all participants throughout the trial.

The data collected will include:

- Reasons and duration of hospitalizations and ED visits.
- Length (hours) of stay in ED per visit.
- Unscheduled visits for urgent care primarily related to COPD symptoms.
- Total length (hours) of stay in ED over the 28-day Treatment Assessment Period.
- ICU admission rate.
- Time to ready-for-discharge in hospitalized participants based on clinical assessment and lung function tests.

The data collected will exclude procedures, tests, and encounters mandated by the protocol.

10.6.1. Time to Ready-for-Discharge in Hospitalized Participants

For hospitalized participants, Investigators or their designees will assess participants daily during the initial hospitalization against the pre-defined discharge criteria based on clinical assessment (eg, normalization of acidosis, symptoms returning to manageable levels). The time required to meet these criteria will be used to evaluate the speed of initial recovery from COPD exacerbation in hospitalized participants.

This assessment applies only to hospitalizations due to the initial COPD exacerbation and is not applicable to hospitalizations resulting from subsequent COPD exacerbations.

11. ASSESSMENT OF SAFETY

11.1. Screening and Eligibility Assessments

Participants who consent to participate in the trial while in a stable condition should complete Screening Visit 1a after providing written informed consent and after their eligibility has been verified. Investigators or their designees will contact the participants by telephone approximately every 4 weeks after Screening Visit 1a to collect any changes in concomitant medications and any SAEs. If a participant's symptoms worsen, such as increased breathlessness, cough, wheeze, chest tightness, sputum production, or sputum discoloration, this may indicate that the participant is experiencing an exacerbation. Participants should be reminded to contact the site to report worsening symptoms at the onset of the exacerbation, before taking any medication. They should then visit the ED or urgent healthcare clinic associated with the trial center to complete Screening Visit 1b (exacerbation visit) and further verify eligibility criteria. Written informed consent, HIPAA authorization, participant demographics, and previous medical and surgical history will not be collected again at Screening Visit 1b. However, medical conditions that started after Screening Visit 1a should be collected.

For participants who consent to participate in the trial during an urgent healthcare visit for an acute COPD exacerbation, Screening Visit 1b should be completed immediately after providing written informed consent and verifying eligibility.

11.1.1. Chest X-ray or CT

A chest X-ray (or CT scan), for purposes of determining participant eligibility, will be performed only at Screening Visit 1b. The maximum combined number of chest X-rays and/or CT scans must not exceed 2 for screening.

11.1.2. Smoking Status Review

At the Screening Visits 1a and 1b, information on smoking history (including cigarettes, electronic cigarettes, pipes, marijuana, vaporizers, and cigars), smoking duration (in years), and smoking quantities (in pack-years) will be collected. Former smokers are defined as individuals who have stopped smoking for at least 6 months prior to Screening Visit 1b. The number of pack-years will be calculated using the formula:

Number of pack years = (number of cigarettes per day / 20) × number of years smoked)
(eg, 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years both equal 10 pack-years)

Recent smoking status will be reviewed at timepoints specified in the SoA (Table 5).

11.1.3. Concomitant Medications

Concomitant medication assessments should include prior or current information regarding all prescription, illicit, nonprescription, or alternative medications (including herbal products, vitamins, and contraceptive medications). Use of any palliative or supportive care medications (eg, analgesics, anti-emetics, antidiarrheals, hematopoietic growth factors, transfusions) should be noted.

See Section 8.2 for more information.

11.1.4. Demographic/Medical and Surgical History and Other Baseline Characteristics

Demographic information collected will include age and sex, along with ethnicity and race as described by the participant. Other baseline characteristics include height, weight, and body mass index. Medical history includes COPD history, acute exacerbation history, past and current medical conditions (such as cardiovascular and cerebrovascular medical history and surgical history), and substance usage.

11.2. Safety Parameters

Safety will be evaluated by assessment of reported AEs, including SAEs and AESIs, DILI, UADEs, safety laboratory evaluations (hematology, clinical chemistry, and urinalysis), vital signs, physical examinations including injection site evaluation, oxygen saturation detected via pulse oximetry, ECG, and concomitant medication/treatment review. The planned timepoints are provided in the SoA (Table 5).

At baseline (Visit 2 Day 0), participants will be monitored for a minimum of 2 hours after IP administration.

11.2.1. Vital Signs and Oxygen Saturation

Vital signs, including body temperature, respiratory rate (breath per minute), pulse (beats per minute), and blood pressure (BP; mmHg), will be measured in the seated position following at least 5 minutes rest at the timepoints specified in the SoA (Table 5).

BP and pulse measurements will be assessed with a completely automated device whenever possible. Manual techniques will be used only if an automated device is not available. Vital signs will be measured prior to the spirometry maneuvers.

Oxygen saturation will be measured by pulse oximeter as indicated in the SoA.

Participants will be monitored for a minimum of 2 hours after IP administration. Vital sign measurements will be performed at 30 minutes (±10 minutes) post-injection and then at 1 hour (±10 minutes) and 2 hours (±15 minutes) post-injection as indicated in the SoA. Any abnormal findings that are new or worsened in severity and clinically significant, in the opinion of the Investigator, will be recorded as an AE. Vital sign measurements will be recorded in the eCRF.

11.2.2. Height and Weight

Height and weight will be measured at time points per the SoA (Table 5). Height will only be measured at Screening Visit 1a or 1b. The participant's height must be measured without shoes and weight must be determined in indoor clothing and without shoes.

11.2.3. Physical Examination

Complete and symptom-directed physical examinations will be performed at timepoints per the SoA (Table 5).

A complete physical examination will cover general appearance, dermatology, head, ears, eyes, nose, throat, respiratory, cardiovascular, abdominal, neurological, musculoskeletal, and lymphatic body systems.

Symptom-directed physical examinations can be performed at the Investigator's discretion at timepoints allowed per the SoA.

Findings from physical examinations will be documented in the appropriate sections of the eCRF. Abnormal findings identified during physical examination will be evaluated and documented by the Investigator as to whether the abnormality is an AE or medical history.

11.2.4. Electrocardiograms

Twelve-lead ECGs will be taken at timepoints per the SoA (Table 5).

ECGs will be taken using an approved ECG machine. It is recommended that the same ECG machine is used for each assessment. The ECG measurements are collected and assessed at local sites.

All ECG measurements will be performed with the participant resting in a supine position for approximately 5 minutes before each reading and should be carried out after measurement of vital signs and before spirometry. ECGs should be performed before blood is drawn during visits requiring blood draws.

The following parameters will be recorded:

- Ventricular rate.
- PR interval.
- QRS duration.
- RR interval.
- QT interval.
- QT interval corrected for heart rate using Fridericia's formula (QTcF).

Note: The QTcF will be centrally calculated for standardization of reporting across all centers.

The Investigator/Investigator's designee will be responsible for reviewing the ECG to assess whether it is within reference limits and to determine the clinical significance of all abnormal ECG results ('clinically significant' or 'not clinically significant'). A copy of the ECG assessment must be kept in the participant's file at the site. The ECG strips or reports will be retained with the source.

11.2.5. Injection Site Reaction Assessment

Assessment of the planned injection sites will be performed prior to dosing and again following the injections prior to release of the participant from the clinic (if applicable), and the additional scheduled timepoints per the SoA (Table 5).

An assessment tool is provided in the Appendix D as an aid in the assessment of common symptoms of injection site reaction. The use of the assessment tool is encouraged but the Investigator may use their own judgement and description of symptoms in the assessment of injection sites following administration of IP.

Participants will be monitored for a minimum of 2 hours after IP administration. Injection sites will be assessed at 30 minutes (±10 minutes) post-injection and then at 2 hours (±30 minutes) post-injection as indicated in the SoA (Table 5).

Prior to the participant being discharged from the clinic visit, the injection sites should be observed, and the participant queried for the following:

- Pain.
- Erythema/redness.
- Itching/scratching/pruritus.
- Warm to touch.

Additionally, when the participant returns for their next visit, the site staff should inquire about any signs/symptoms of an injection site reaction that occurred after discharge from the prior clinic visit.

An injection site reaction should be reported as an AE if the Investigator judges the reaction as clinically significant. If the AE of Injection Site Reaction lasts longer than 24 hours and the severity is Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3, it will be considered an AESI as defined in Section 11.3.3 and should be reported as described in Section 11.7.2.

See Appendix D for an injection site reaction assessment tool.

11.2.6. Laboratory Assessments

Safety laboratory samples (hematology, clinical chemistry, urinalysis) will be performed at visits according to the SoA (Table 5). See Appendix C for the list of clinical laboratory tests to be performed.

Standard laboratory hematology, clinical chemistry, and urinalysis will be analyzed by a qualified central laboratory. Any safety laboratory tests completed as part of the assessment and treatment of the COPD exacerbation may be used for Screening (eg, clinical chemistry, hematology, urinalysis).

Due to the short screening window, local laboratory results will be used for the purpose of determining the participant's eligibility for randomization. Local laboratory samples should be taken at Screening V1b and the results should be received and reviewed prior to randomization to allow review of the applicable eligibility criteria. If local laboratory results from the assessment of the current COPD exacerbation are already available within 48 hours prior to Screening V1b, these results can be used for determination of participant's eligibility. For all randomized participants, a sample for central laboratory analysis should be obtained before IP administration on Day 0 as baseline.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the trial in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the trial or within 28 days after the dose of IP should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

11.2.7. Pregnancy Screen

Pregnancy screening for females of childbearing potential must be negative prior to IP administration. Pregnancy tests will be analyzed at a local laboratory.

A serum pregnancy test must be taken at Screening (Visits 1a and/or 1b) in women of childbearing potential (WOCBP) as described in the SoA (Table 5). A urine pregnancy test (human chorionic gonadotropin; dipstick) must be performed at the trial site at baseline prior to randomization in WOCBP, unless the Baseline Visit (Day 0) and Visit 1b are on the same day. The test must be repeated every 4 weeks as shown in the SoA (Table 5).

Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the trial.

Pregnancy reporting requirements are found in Section 11.7.5 .

11.3. Safety Reporting Definitions

Investigators are responsible for the detection and documentation of events that meet the definition of an AE, SAE, AESI, suspected DILI, or UADE, as provided in this protocol.

Investigators must review the Investigator's Brochure so as to be aware of the safety-related events, which may be anticipated with its use. Investigators should also be versed in the latest standard of care guidelines.

11.3.1. Adverse Event (AE)

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE may be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not considered causally associated with the use of the IP. Any abnormal laboratory value, vital sign result, or ECG or X-ray finding deemed clinically significant by the Investigator, regardless of causal relationship, must be reported as an AE. A clinical diagnosis, rather than the changes in laboratory analyte or other assessment, should be recorded (eg, anemia rather than low hemoglobin value).

Examples of AEs include the following:

- Significant or unexpected worsening or exacerbation of the condition or indication under study (eg, acute COPD exacerbation as diagnosed from signs and symptoms such as cough frequency and severity, sputum production, dyspnea).

- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency or intensity of the condition (eg, abnormal physical examination finding).
- Signs, symptoms, or clinical sequelae of a suspected interaction.
- Signs, symptoms, or clinical sequelae of a suspected overdose of the IP or a concurrent medication (overdose per se should not be reported as an AE or SAE, unless nonserious or serious sequelae [respectively] occur).
- The following abnormal laboratory results:
  - Any laboratory abnormality suggestive of a new disease/organ toxicity or a worsening of a pre-existing condition.
  - Any laboratory abnormality that required the participant to have IP interrupted or discontinued.
  - Any laboratory abnormality that required the participant to receive specific treatment for the lab abnormality.
  - Any laboratory abnormality that required additional monitoring and follow-up visits.
  - Any laboratory abnormality requiring further diagnostic investigation.

The following examples are not considered AEs:

- Medical or surgical procedure (eg, endoscopy, appendectomy), although the condition that leads to the procedure is an AE.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) (including laboratory values) present or detected at the start of the trial that do not worsen.
- The disease or disorder being studied, or expected progression, signs, or symptoms of the disease or disorder being studied, unless they become more severe or occur with a greater frequency than expected for the participant's condition.

11.3.2. Serious Adverse Event (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening AE (ie, presented an immediate risk of death from the event as it occurred. This criterion is not intended to include an AE that, had it occurred in a more severe form, might have caused death.)
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The following events do not meet the definition of an SAE: hospitalization for elective treatment of a pre-existing condition that does not worsen from baseline, hospitalizations for a standard procedure for IP administration, routine monitoring of the studied indication not associated with any deterioration in condition, social or convenience admission to a hospital, prolongation of a hospitalization for social or convenience reasons not associated with the occurrence of an AE, or hospitalization or an emergency room visit that lasts less than 24 hours that does not meet the criteria of an important medical or a life-threatening event.

11.3.3. Adverse Event of Special Interest (AESI)

An AESI may be serious or non-serious and is one of scientific and medical concern specific to the Sponsor's product mechanism of action, for which ongoing monitoring may be appropriate. Such an event might warrant further investigation to characterize and understand it and rapid communication by the trial Sponsor to other regulatory authorities may also be warranted.

For this trial, AESIs shall include:

- Conjunctivitis
- Keratitis
- Severe injection site reactions persisting for more than 24 hours: defined as injection site reactions persisting for more than 24 hours and the severity is CTCAE Grade ≥3.
- Parasitic and opportunistic infections: whether the infection is classified as opportunistic infection will be determined after discussion with medical monitor. When reporting opportunistic infection, the Investigators will refer to Appendix J Table 7.
- Anaphylaxis: defined according to the symptoms shown in Appendix J Table 8.

11.3.4. Suspected Drug-induced Liver Injury (DILI)

DILI refers to a liver injury induced by various chemical drugs, biological products, herbal medicines and their metabolites or even excipients. Hy's Law can facilitate assessment of severe liver injury predominated by hepatocellular injury. It specifically refers to cases that meet all of the following 3 criteria:

For participants with normal liver function tests at baseline:

1. ALT or AST ≥ 3× ULN during Treatment Assessment Period, and

2. Total bilirubin > 2× ULN during Treatment Assessment Period; without cholestasis at baseline (serum alkaline phosphatase [ALP] increased), and
3. No other identifiable causes explaining the simultaneous elevation of aminotransferases and total bilirubin, such as viral hepatitis A, B, C or E or other acute liver diseases, or concomitant use of other drugs that may induce liver injury.

11.3.5. Unanticipated Adverse Device Effect (UADE)

According to 21 CFR 812.3(s), a UADE means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

11.3.6. Unexpected Adverse Event

An AE that is not listed in the IB at the specificity or severity that has been observed. For example, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. This includes AEs that are mentioned in the IB as occurring with a class of products or as anticipated from the pharmacological properties of the IP but are not specifically mentioned as occurring with the particular IP under investigation.

11.4. Relationship to Investigational Product

The Investigator will assess the relationship of each AE to IP based on his/her clinical judgment. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The Investigator's assessment of an AE's relationship to IP is part of the documentation process, but it is not a factor in determining what is or is not reported in the trial. The Investigator will assess causality for every event before entering information into the AE eCRF/Safety Reporting Form. The Investigator may change his or her opinion of causality in light of follow-up information and amend the AE/SAE information accordingly in the eCRF or the AE eCRF/Safety Reporting Form, as applicable. The Sponsor's assessment of relationship may differ from the Investigator's assessment.

Relationship to IP will be assessed according to the following guidelines:

- Possibly related: the AE is known to occur with the IP, there is a reasonable possibility that the IP caused the AE, or there is a temporal relationship between the IP and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the IP and the AE.
- Unlikely related: there is not a reasonable possibility that the administration of the IP caused the event, there is no temporal relationship between the IP and event onset, or an alternate etiology has been established.

11.5. Severity Assessment

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 11.3.2. An AE of severe intensity may not be considered serious.

The Investigator may use the CTCAE Version 5.0 to assist in the determination of severity and clinical significance. The following represents CTCAE grading of AE severity:

- Grade 1: asymptomatic or mild symptoms or clinical or diagnostic observations only or intervention not indicated.
- Grade 2: minimal, local or noninvasive intervention indicated or limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3: hospitalization or prolongation of hospitalization indicated or disabling or limiting self-care ADLs. Self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.
- Grade 4: Life-threatening consequences with urgent intervention indicated.
- Grade 5: Death related to AE.

11.6. Recording Adverse Events

All AEs regardless of causality will be recorded in the EDC from the time the participant signs the ICF through the participant's last visit or 28 days post last dose, whichever is longer. AEs that occur after signing of the ICF but prior to IP administration should be recorded on the Medical and Surgical History eCRF. AEs reported during this time that are serious should also be reported as an SAE (Section 11.7.1). Any clinically significant findings as determined by the Investigator, or changes from the time of signing the ICF, should be recorded on the AE or Medical History eCRF, as applicable.

For participants who received IP, if an Investigator becomes aware of an SAE that occurs after the participant’s trial participation ends and the Investigator considers the event to be possibly related to the IP, the Investigator should report the SAE to the Sponsor as described in Section 11.7.1.

11.7. Safety Reporting to the Sponsor of Serious Adverse Events and Other Safety Reports

11.7.1. Serious Adverse Events

If the Investigator determines that an event meets the protocol definition of an SAE due to any cause that occurs during the course of this trial, regardless of relationship to IP, he/she must notify the Sponsor by entering the SAE information into the eCRF within 24 hours of the Investigator becoming aware of the SAE.

If EDC is not available, the Investigator must complete a Safety Reporting Form and email it to the Sponsor **within 24 hours** of the Investigator becoming aware of the SAE. The Investigator must also enter the SAE information into the eCRF as soon as possible thereafter.

Sponsor Safety Reporting Email Address: connectsafety.sm@thermofisher.com

In the initial email, the Investigator must provide to the Sponsor the following eCRF pages, completed to the greatest extent possible:

- AE record.
- Medical history.
- Prior and concomitant medications.

Also, the following documents are to be forwarded: any laboratory results, diagnostic test results, or medical reports relevant to the SAE.

The EDC is the primary method for notification of SAE information. In rare circumstances and in the absence of email capacity, notification by fax or telephone is acceptable, with a copy of the Safety Reporting Form sent by overnight mail. Initial notification via telephone does not replace the need for the Investigator to complete the SAE information in the eCRF within the time frames outlined.

If the Investigator does not have all information regarding an SAE, he/she must not wait to receive additional information before notifying the Sponsor of the event. The SAE must be updated when additional information is received. Follow-up information received on all SAEs must be forwarded to the Sponsor using the same timelines as for an initial report.

11.7.2. Adverse Event of Special Interest

The Investigator must notify the Sponsor of any AESI that is serious (ie, an SAE) **within 24 hours** of the Investigator becoming aware of the event following the same reporting process as outlined for SAEs in Section 11.7.1.

For an AESI that does not meet the definition of an SAE, the Investigator must report it to the Sponsor **within 72 hours** of becoming aware of the event and following the same reporting process as outlined for SAEs in Section 11.7.1 by entering the information on the eCRF or utilizing the Safety Reporting Form, if the EDC is not available.

11.7.3. Drug-induced Liver Injury

The Investigator must notify the Sponsor **within 24 hours** of awareness that a participant has experienced DILI suspected to meet the Hy's Law following the same reporting process as outlined for SAEs in Section 11.7.1. The recommendations for the follow-up and handling of suspected DILI cases are provided in Appendix K.

11.7.4. Unanticipated Adverse Device Effect

The Investigator must notify the Sponsor of any UADE. If a UADE is associated with an SAE, the Investigator must notify the Sponsor **within 24 hours** of the Investigator becoming aware of the effect following the same reporting process as outlined for SAEs in Section 11.7.1.

11.7.5. Reporting Pregnancy

Pregnancy is not considered to be an AE; however, if the outcome of a pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion includes miscarriage and missed abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the Investigator should follow the procedures for reporting SAEs . Female participants who become pregnant within 8 weeks after receiving IP should also notify the Investigator. The Investigator must attempt to follow the pregnancy to term or termination to report on outcome and health status of mother and child.

The Investigator must notify the Sponsor of any pregnancy by completing a Pregnancy Form and emailing it to the Sponsor **within 24 hours** after the Investigator becomes aware of the pregnancy.

Sponsor Safety Reporting Email Address: connectsafety.sm@thermofisher.com

11.8. Follow-Up of Adverse Events

After the occurrence of an AE, the Investigator is required to follow each participant proactively and provide further information on the participant's condition. All AEs documented at a previous visit or contact and designated as ongoing will be reviewed at subsequent visits or contacts.

Nonserious AEs will be followed after the last scheduled trial visit until the event resolves, the condition stabilizes, or until the event is otherwise explained or judged by the Investigator to be no longer clinically significant (unless the participant is lost to follow-up or withdraws consent).

SAEs will be followed until the event resolves (ie, when the event no longer meets any of the seriousness criteria), the condition stabilizes, or until the event is otherwise explained or judged by the Investigator to be no longer clinically significant (unless the participant is lost to follow-up or withdraws consent). The Investigator will ensure that follow-up information provided to the Sponsor includes results of any additional laboratory tests or investigations, histopathologic examinations, or consultations with other healthcare professionals that serve to clarify the nature of the event, the cause of the event, or both. New or updated information will be recorded as outlined in the section Reporting Serious Adverse Events to the Sponsor (see Section 11.7.1).

The Investigator will assess the outcome of each AE using the following categories:

- Resolved/Recovered: the AE resolved or the participant recovered without sequelae. An AE (either serious or nonserious) occurred and had an end date without a complication.
- Resolved/Recovered with sequelae: the AE has a complication or condition that results from a previous AE.
- Not resolved: at the end of the trial, a nonserious AE either has not changed in intensity or may not have recovered to baseline values.
- Unknown: the participant has withdrawn from the trial prematurely or is lost to follow-up, and the status of the event is unknown.
- Death.

12. PHARMACOKINETICS AND PHARMACODYNAMICS

12.1. Pharmacokinetics

Blood samples for PK assessments will be collected prior to administration of IP and post-dose at the specified timepoints (Table 5). Plasma samples for determination of rademikibart concentrations will be analyzed by a laboratory using a validated method.

Whole blood samples of approximately 2 mL will be collected and processed for measurement of plasma concentrations of rademikibart. Each plasma sample will be divided into 2 aliquots (1 for PK, and a backup).

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

12.2. Pharmacodynamics

Biomarkers of type 2 inflammation will be assessed over the course of participants' treatment including blood eosinophil count, eotaxin-3, C-reactive protein (CRP), total immunoglobulin E (IgE), and TARC as specified in the SoA (Table 5). Additionally, pulmonary and activation-regulated chemokine (PARC) and fibrinogen will be assessed.

Blood will be collected for measurement of these biomarkers of inflammation associated with COPD as specified in the SoA.

12.2.1. Fractional Exhaled Nitric Oxide

FeNO will be measured using a NIOX VERO® Airway Inflammation Monitor, or equivalent device according to the SoA (Table 5). The FeNO test will be performed prior to spirometry. Participants should not eat or drink for 1 hour prior to having the FeNO test.

Further details on the procedure for measuring FeNo with NIOX will be provided in a separate instruction manual

12.3. Immunogenicity

Immunogenicity will be evaluated by assessment of anti-drug antibodies (ADAs) and, if applicable, neutralizing antibodies (nAbs) according to the SoA (Table 5).

Antibodies to rademikibart will be evaluated in serum samples collected from all participants. Additionally, serum samples should also be collected at the final visit from participants who were withdrawn from the trial. These samples will be tested by the Sponsor's designee using validated methods.

Serum samples will be screened for ADAs binding to rademikibart and the titer of confirmed positive samples will be reported. Confirmed positive samples will be assessed for nAb and reported as nAb positive/negative.

12.4. Blood Volumes

Blood samples will be drawn for safety (hematology, clinical chemistry), PK, PD, immunogenicity (ADAs, nAbs), and biomarkers. The total volume of blood to be withdrawn is

approximately 135.5 mL, which is less than the volume of blood drawn during a blood donation (~500 mL).

13. STATISTICS

Complete details of the statistical analyses and methods, including data conventions, will be contained in a separate Statistical Analysis Plan (SAP) that will be finalized before database lock and unblinding. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

13.1. Primary Analysis Hypothesis

The null hypothesis is that there is no difference in the treatment failure rates between rademikibart treatment and placebo (rademikibart vs placebo).

H_0: P_(rademikibart)- P_p=0, where P_(rademikibart) and P_p are the proportion of participants with treatment failure within 28 days after randomization for those randomized to rademikibart and placebo, respectively.

The alternative hypothesis is that rademikibart is different from placebo with respect to the treatment failure rate within 28 days after randomization.

H_a: P_(rademikibart)- P_p≠0.

13.2. Sample Size Determination

Approximately 160 participants with COPD exacerbation will be randomized using 1:1 allocation ratio to rademikibart 600 mg SC or placebo. The sample size calculation is based on the statistical analysis of the primary endpoint of treatment failure rate.

To account for a 5% dropout rate, approximately 160 participants will be randomized to ensure that 152 participants are evaluable. Assuming treatment failure rates of 22.5% for the rademikibart group and 45% for the placebo group up to 28 days after randomization, this sample size will provide at least 80% power to detect a difference at a 2-sided Type I error rate of 5%. Conditional power will be calculated during the IA and the final sample size will be determined according to the prespecified rules.

To ensure that the sample size is reasonably sufficient, an unblinded sample size re-estimation will be conducted when approximately the first 80 participants in total have had the opportunity to complete the trial or discontinue early (ie, no ongoing participants will be included in this sample size re-estimation procedure). The unblinded sample size re-estimation procedure for this trial will not allow for a reduction in the planned sample size or an increase in sample size greater than 40 participants per group (80 participants total). This sample size re-estimation procedure will be conducted by a statistician who is not associated with the conduct or final analysis of the trial. No penalty will be applied to the p-values or confidence intervals for assessing treatment difference from placebo due to this sample size re-estimation procedure. The independent statistician and DMC will recommend to the Sponsor any changes required to the sample size. Results from the IA will be communicated to a limited number of the Sponsor’s senior management team who are independent of the clinical trial team and will be identified in the unblinding plan before the IA is performed.

13.3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Analysis Set	Description
RS	All participants who are randomized to treatment.
FAS	All participants from RS having taken at least 1 dose of IP after randomization; data will be presented based on randomized treatment group.
PPS	All participants from FAS without important protocol deviation(s) that could affect the evaluation of the IP.
SS	All participants from RS having taken at least 1 dose of IP after randomization; data will be presented based on treatment actually received.
PKS	All participants from RS with at least 1 dose of rademikibart taken and with at least 1 post-dose evaluable PK blood sample.

FAS = Full Analysis Set; IP = investigational product; PKS = Pharmacokinetics Analysis Set; PPS = Per-Protocol Set; RS = Randomized Set; SS = Safety Analysis Set

All screened participants will be accounted for in the clinical study report (CSR). The inclusion and/or exclusion of participants from the trial analysis sets will be documented in the SAP before breaking the randomization code.

Participants in the Randomized Set (RS) will be summarized according to the treatment group to which they were randomized.

Participants in the Full Analysis Set (FAS) will be summarized according to the treatment group to which they were randomized, regardless of treatment received. The primary analyses of all efficacy endpoints will be conducted in the FAS.

Supportive efficacy analyses will be conducted in the Per-Protocol Set (PPS). Analyses based on the PPS will be performed to support the results obtained for the FAS. Reasons for exclusion from the PPS will be documented prior to database lock and unblinding.

The analysis population for the safety endpoints will be the Safety Analysis Set (SS). These participants will be analyzed according to their actual treatment received, regardless of the randomized treatment assigned.

The analysis population for the immunogenicity endpoints will be the subset of Pharmacokinetic Analysis Set (PKS) population with at least a predose (baseline) and at least one evaluable post-dose immunogenicity assessment.

13.4. Statistical Analyses

13.4.1. General Considerations

Unless otherwise stated, all significance tests will be 2-sided using the 5% significance level. In addition, 95% confidence intervals will be provided where appropriate.

An observed-cases approach will be used for tabulations of data by visit (ie, involving only those participants who attended each specific visit).

Categorical data will be summarized using the number and percentage of participants in each category and treatment group. Continuous data will be summarized using descriptive statistics including the number of non-missing observations (n), mean, standard deviation, minimum, 25th percentile, median (50th percentile), 75th percentile, and maximum values.

All the analyses specified in the protocol will be reviewed in relation to the blinded data obtained and the SAP will be finalized before breaking the randomization code for primary analysis. Any changes from the statistical analysis planned in this clinical trial protocol will be described and justified in a protocol amendment, the SAP, and/or in the CSR.

Objectives and endpoints are provided in Section 5.

13.4.2. Multiplicity Adjustment

The analysis of secondary and exploratory endpoints will not have multiplicity adjustments.

13.4.3. Disposition of Participants

Participant disposition will be presented, including reasons for discontinuation from the trial, for all participants who provide informed consent.

13.4.4. Demographics and Other Baseline Characteristics

Demographics include age, sex, race, and ethnicity. Other baseline characteristics include height, weight, duration of COPD, past and concurrent diagnoses (from medical history and indications for concomitant medications), concomitant medications, previous COPD treatments, and substance usage.

Descriptive statistics of demographics and other baseline characteristics will be presented separately for all randomized participants, the FAS, and the PPS. The presentations will be overall and by treatment group. Demographics and other baseline characteristics will also be listed.

13.4.5. Primary Efficacy Endpoint

Formal hypothesis testing will be performed to analyze the difference in treatment failure rates between treatment groups within 28 days after randomization using the Cochran-Mantel-Haenszel test for the common risk difference stratified by severity of acute COPD exacerbation and baseline smoking status. The risk difference and the corresponding 95% CI will be presented. The null hypothesis of no difference in response rates between rademikibart and placebo will be tested against the 2-sided alternative that there is a difference at significance level 0.05. The primary efficacy analysis will be conducted based on observed data using the FAS.

13.4.5.1. Sensitivity Analyses

Sensitivity Analysis 1: Missing data from participants who discontinue the trial prior to a documented treatment failure will be considered to have experienced treatment failure. The primary analysis will be repeated using this sensitivity analysis to handle missing data.

Sensitivity Analysis 2: Tipping point analyses will be conducted whereby the primary analysis on the binary endpoint will be repeated for every possible scenario regarding the missing

endpoints. Every possible combination of response and non-response in the Rademikibart dose and placebo groups is considered for the missing values, and the primary analysis is repeated for each scenario. A plot of p-values will be provided, and the robustness of the primary result will be assessed.

13.4.5.2. Supplementary Analyses

The primary analysis will be repeated on PPS.

13.4.6. Secondary Efficacy Endpoints

The rate of moderate and severe COPD exacerbations in the 28 days after randomization will be analyzed using a negative binomial regression model adjusting for randomization stratification factors and baseline characteristics. Full details of the model will be documented in the SAP.

The time to the first moderate or severe COPD exacerbation will be analyzed using a stratified log-rank test, adjusting for the randomization stratification factors. A Kaplan-Meier plot of the time to first moderate or severe COPD exacerbation will be provided.

A mixed model repeated measures analysis will be used to compare treatment groups with respect to the mean CFB in E-RS: COPD through Week 1, Week 2, and Week 4; and with respect to the absolute CFB in post-BD FEV_1 at Day 3, Week 1, and Week 4. The mixed model repeated measures model will include fixed factors for scheduled visit, treatment, the visit by treatment interaction, and will include covariates for the stratification factors and the respective baseline value of the continuous outcome. An unstructured covariance matrix will be used to model the within-participant covariance structure.

The FAS will be used for the secondary endpoint analyses.

13.4.6.1. Supplementary Analyses

Analysis for key secondary endpoint will be repeated on PPS.

13.4.7. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are provided in Section 5.

Exploratory efficacy endpoints will be summarized by treatment group and visit using descriptive statistics. Cochran-Mantel-Haenszel chi-square tests will be used to compare treatment groups with respect to the proportion-based binary efficacy endpoints and a mixed model repeated measures or analysis of covariance will be used to compare treatment groups with respect to continuous efficacy endpoints. Negative binomial models will be used for any exploratory analyses of exacerbation rates, and stratified log-rank test will be used for any time-to-event driven exploratory analyses. Analyses will be conducted based on observed data using the FAS.

13.4.8. Safety Analysis

The safety endpoints are provided in Section 5.

The analyses of safety will be based on the SS.

Safety data will be summarized using frequency tables (counts with percentages) and will be presented by treatment and scheduled time, if appropriate. Continuous safety data will be summarized using descriptive statistics by treatment and scheduled visits and timepoints, if applicable.

Summaries will be provided by scheduled visit and time point. Data collected at unscheduled times will be listed but will not be included in summaries by scheduled visit.

Safety endpoints to be summarized include AEs, injection site reactions, vital signs (BP, pulse, respiratory rate, and temperature), ECG parameters, and safety laboratory data (hematology, clinical chemistry, and urinalysis).

13.4.8.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities. TEAEs are defined as any AEs that occur or worsen during the Treatment Assessment Period, whether or not considered related to the treatment. The incidence of TEAEs will be presented overall, by system organ class, and by preferred term (PT) for each treatment group. Incidence of TEAEs by severity and relationship to IP will also be presented for each treatment group. Deaths, SAEs, AESIs and AEs resulting in discontinuation from the IP or trial will be summarized by treatment group.

In addition, AEs occurring during the Follow-up Period will be summarized for participants followed during that period.

A listing will be provided for all participants who experience a TEAE, SAE, discontinue IP or trial prematurely because of AEs, and temporarily interrupt IP because of AEs. AESIs will also be listed.

13.4.8.2. Concomitant Medications

Medication names will be coded according to the World Health Organization Drug Dictionary. Prior and concomitant medications will be summarized overall and by drug classification and preferred name by treatment group.

Prior medications summaries will be restricted to medications stopped before the date of first IP dose. The summary of concomitant medications will comprise all medications taken during the Treatment Assessment Period, including medications ongoing at entry.

13.4.8.3. Vital Signs

The change in vital signs (BP, pulse, respiratory rate, body temperature) from baseline to each visit will be summarized by visit and treatment group descriptively including mean, standard deviation, minimum, 25^{th} percentile, median (50^{th} percentile), 75^{th} percentile, and maximum values. The number and percentage of participants with a treatment-emergent potentially clinically significant values will be summarized.

13.4.8.4. Laboratory Values

The change in each of the laboratory parameters from Baseline to each visit will be summarized by visit and treatment group descriptively including mean, standard deviation, minimum, 25^{th} percentile, median (50^{th} percentile), 75^{th} percentile, and maximum values.

Laboratory parameters will be classified as 'low', 'normal', or 'high', depending on whether the value is below, within, or above the reference range, respectively. Shift tables based on the low/normal/high categories may be produced showing the categories at Baseline against those at each visit. Listings with laboratory parameters outside the reference range flagged will be provided.

13.4.8.5. ECG Data

Ventricular rate, RR interval, QT interval, QTcF, PR interval, and QRS duration values at each timepoint, and CFB at each timepoint after first dose will be summarized. The number and percentage of participants with a treatment-emergent potentially clinically significant ECG value will be summarized. A listing of participants with extreme values or changes will be provided.

13.4.9. Anti-drug Antibodies

ADA status (positive vs negative) at each visit will be summarized by treatment group. If considered relevant, descriptive statistics including number of participants, mean, standard deviation, median, and range of the actual ADA titers by treatment group and visit will be provided. The ADA status across the trial for each participant (positive vs negative) will also be classified and summarized by treatment group.

The association of ADA status across the trial (positive vs negative) with AEs/SAEs may be evaluated. In addition, the association of ADA titers (≥ median titer in positive participants vs < median titer) with AE/SAEs may be evaluated for ADA-positive treated participants only. The ADA-positive participants across the trial may also be divided into persistent positive vs transient positive. A participant will be considered as persistent positive if he/she has positive ADA for ≥2 consecutive visits with ADA assessment. Otherwise, the participant will be considered as transient ADA-positive. The associations between ADA and AE/SAEs may be summarized for both persistent positive participants vs transient positives participants.

Evaluations of nAb will be conducted on those serum samples that test positive for ADA. The test sample is deemed positive or negative for the presence of nAb to rademikibart relative to a predetermined (in assay validation), statistically derived cut point.

All participants with titer information will be listed.

13.4.10. Pharmacodynamic Analysis

Biomarker analyses will be considered exploratory. Changes of serum levels of PD analytes and peripheral eosinophil counts will be summarized using descriptive statistics by treatment and scheduled time and, if appropriate, will be plotted by treatment. Exploratory biomarker analyses will be detailed in a separate analysis plan and report.

13.4.11. Pharmacokinetic Analysis

Whole blood for plasma rademikibart concentrations will be obtained and analyzed as per the SoA (Table 5). Individual plasma concentrations will be plotted and summarized using descriptive statistics by scheduled time.

Rademikibart PK data from this trial will be pooled with data from other studies to inform the population PK model of rademikibart in this trial population. Results of the population PK analysis will be reported separately.

13.5. Other Analysis

13.5.1. Subgroup Analysis

Subgroup analyses of the primary endpoint and secondary endpoints will be conducted to assess consistency of the investigational intervention effect across the following subgroups:

- Sex.
- Race.
- Ethnicity.

If the number of participants is too small within a subgroup, then the subgroup categories may be redefined before unblinding the trial. Forest plots presenting the estimated trial arm difference and 95% CIs will be provided. Further details on the statistical analysis will be provided in the SAP.

13.6. Handling of Missing Data

Missing data handling is described in the Sensitivity Analyses for primary endpoint in Section 13.4.5.1.

Additional details will be provided in the SAP.

13.7. Interim Analysis

One IA is planned to be performed when approximately 80 participants with an acute COPD exacerbation have completed the Week 4 Visit. This analysis will allow for the potential adjustment of the sample size.

During the IA, the treatment failure rate will be assessed, the COPD exacerbation rate over the 4-week period will be assessed, and conditional power will be calculated by an independent statistician. The independent statistician will compare the calculated conditional power with the prespecified sample size and estimate the final sample size for the trial. The independent statistician and DMC will recommend to the Sponsor any changes required to the sample size. Results from the IA will be communicated to a limited number of the Sponsor's senior management team independent of the clinical trial team; these people will be identified in the unblinding plan before the IA are performed.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Trial Monitoring

Before an investigational site can enter a participant into the trial, a Sponsor representative will visit the investigational trial site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Trial Agreement between the Sponsor and the Investigator.
- The Sponsor (or its designee) is responsible for ensuring the proper conduct of the trial. This includes ensuring the participants' rights and well-being are protected, the conduct of the trial is within compliance of an approved protocol and GCPs, and the integrity of the data are accurate, complete and verifiable from source documentation. At regular intervals during the trial, the Sponsor or its designees will contact the trial site via site visits, telephone calls, emails, and letters to review trial progress and the eCRF completion and to address any concerns or questions regarding the trial conduct. The extent, nature, and frequency of on-site visits will be based on such considerations as the trial objectives and/or endpoints, the purpose of the trial, trial design complexity, and enrollment rate. During monitoring visits, the following aspects of trial conduct will be carefully reviewed: participants' informed consent documents, participant recruitment procedures, participants' compliance with the trial procedures, source-data verification, drug accountability (unblinded monitor only), use of concomitant therapy by participants, AE and SAE documentation and reporting, and the quality of data. By signing the protocol, the Investigator agrees to Sponsor (or designee) monitoring of the trial.

During the trial, a monitor from the Sponsor or representative will have regular contact with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRFs with the participant's medical records at the hospital or practice, and other records relevant to the trial. This will require direct access to all original records for each participant (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.

14.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an IRB/IEC may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Board

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this trial including the participant consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor or its designee establishes quality assurance and quality control systems with Standard Operating Procedures to ensure that the clinical trial is conducted, and the data are generated, documented (recorded), and reported in compliance with the protocol, ICH Guideline for GCP E6, and applicable regulatory requirements.

Investigators are responsible for adhering to GCP guidelines. Investigators must ensure that all data collected during the trial are accurate, complete, and reliable before presenting it to the Sponsor and that it can be used for regulatory submissions. The Investigator or designee must record all required data using the prespecified data collection method defined by the Sponsor or its designee.

15.1. Trial Auditing

The Investigator should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

The Sponsor also reserves the right to audit sites with advanced notice. Sponsor audits may be routine or for-cause. The trial may be audited or inspected at any point during or after completion by the Sponsor (or designee), IEC/IRB, and/or regulatory authorities. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, the competent authority, or other regulatory agencies direct access to all trial records such as the trial protocol, eCRFs, participant consent forms, participant records maintaining confidentiality, AE reports, and source data. The Investigator will immediately notify the Sponsor of all audits or inspections scheduled by any regulatory authority and promptly forward copies of any audit or inspection reports, including any discrepancies, non-compliance, and corrective actions, to the Sponsor.

16. ETHICS

16.1. Ethics Review

16.1.1. Institutional Review Board/Ethics Committee Approval

Federal and national regulations and ICH guidelines require approval be obtained from an IRB/IEC before participation of human participants in research studies. Before the trial onset, the protocol, ICF, advertisements to be used for participant recruitment, and other written information regarding this trial to be provided to the participant or the participant's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH Guideline E6 will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC Chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title and/or protocol number, and the date approval and/or favorable opinion was granted.

The Principal Investigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The Principal Investigator must supply the Sponsor or its designee with written documentation of continued review of the clinical research.

16.2. Ethical Conduct of the Trial

This trial will be conducted in compliance with the protocol and all applicable regulatory requirements in accordance with ICH/GCP and in general conformity with the most recent version of the Declaration of Helsinki.

16.3. Written Informed Consent

The informed consent process for clinical studies must comply with Title 21 of the CFR Part 50, the Declaration of Helsinki, GCP requirements (CPMP/ICH/135/95), and local regulations, with patient protection as priority. Before participation, each participant must sign a written ICF with information on the trial and its potential risks. A separate ICF is needed for genetic analysis if applicable.

If any changes to trial procedures occur at a site, the ICFs must be reviewed by the Sponsor or its designee and approved by the IRB/IEC before use. If the ICF is revised during the trial, all active participants must sign the updated version. The Principal Investigator must ensure that the participant or their legal guardian fully understands the trial before signing the ICF.

The Principal Investigator provides a signed copy to the participant and keeps the original in the participant's medical records. The Sponsor will provide a multicenter ICF template, which may be adapted to conform to institutional needs while ensuring compliance with regulatory requirements. Any amendments or new information that may impact a participant's willingness to join the trial will prompt a revised ICF from the Sponsor.

The ICF must be written in clear, non-technical language to ensure understanding while detailing the trial's purpose, potential risks, benefits, and the participant's right to withdraw at any time

without consequence. After obtaining consent, the ICF is stored in the Investigator's site file and made available for review. Documentation of the informed consent discussion is added to the participant's case history, and each participant receives a copy of the signed ICF. If the ICF is revised, re-consent will be obtained following the same process.

16.4. Investigator Responsibilities

The Investigator is responsible for the following:

- Reading and understanding the current version of the rademikibart IB (version 5 or above).
- Obtaining IRB/IEC review and approval for trial (per 21 CFR 56 [US] and ICH E6.4).
- Ensuring IRB/IEC provides initial and continuing review, and the approval of the trial complies with relevant local regulations (per 21 CFR 56 [US] and ICH E6.4); promptly informing IRB/IEC of changes in research activity or any unanticipated problems involving risk to participants.
- Making no changes to trial without approval by Sponsor and IRB/IEC review and approval (except when needed immediately to protect safety, rights, or welfare of trial participants).
- Notifying trial participants that rademikibart is investigational; obtaining informed consent from each participant per relevant regulations (per 21 CFR 50 [US] and ICH E6.4).
- Informing Sponsor or designee of AEs and unanticipated problems during trial (per 21 CFR 312.64 [US] and ICH E6.4); SAEs, serious AESIs and DILI to be reported within 24 hours.
- Maintaining adequate and accurate records (per 21 CFR 312.62 [US] and ICH E6.4); make records available for inspection (per 21 CFR 312.68 [US] and ICH E6.4).
- Complying with all other pertinent requirements of 21 CFR 312 (US) and ICH E6.4.
- An original Investigator-signed Investigator Agreement page of the protocol
- Providing an IRB/IEC-approved ICF, samples of site advertisements for recruitment, and any other written information regarding this trial that is to be provided to the participant or legal guardians.
- Form FDA 1572 (US) or form with equivalent information, fully executed, and all updates on a newly executed Form FDA 1572 (US) or equivalent.
- Curriculum vitae (CV) for the Principal Investigator and each Sub-Investigator will be listed on Form FDA 1572 (US) or ICH E6.4 or local equivalent. Current licensure must be noted on the CV. These will be signed and dated by the Principal Investigators and Sub-Investigators at trial start-up, indicating they are accurate and current.

- Providing financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54 (US) or relevant local equivalent.
- Providing laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with 42 CFR 493 (US) or relevant local equivalent.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the trial. The Investigator agrees to allow the monitor to inspect the drug storage area, IP stocks, drug accountability records, participant charts and trial source documents, and other records relative to trial conduct.

17.2. Source Documents and Retention of Records

All trial documents and records must be maintained by the Investigator or institution for a specified period, in accordance with ICH E6, Section 8 guidelines. These documents should be stored securely to ensure they are readily accessible for review, inspection, and audit by the Sponsor, regulatory authorities, or CRO. This includes documents from before, during, and after the clinical trial. Examples include the trial protocol and any amendments, Investigator brochure, financial aspects of the trial, insurance statements (if applicable), signed agreements between all parties, eCRF, delegation of authority logs, pharmacy dispensing records, drug accountability logs, AE reports, participant source data (original or certified copies), correspondence with health authorities and IECs/IRBs, ICFs, monitoring visit logs, laboratory certifications or quality control procedures, and laboratory reference ranges. These documents should be stored in either electronic or paper format in a secure location to preserve their integrity, prevent loss, damage, or unauthorized access. Electronic records must comply with 21 CFR 11 requirements to ensure data integrity, authenticity, and accessibility.

The Investigator or Sponsor is responsible for ensuring that trial records are retained for at least two years after the last marketing application approval in an ICH region or until there are no pending or contemplated marketing applications in that region, or until at least 2 years have passed since the formal discontinuation of clinical development for the IP. However, these records should be kept longer if required by applicable regulatory requirements or agreed upon in the Clinical Trial Agreement. It is the Sponsor's responsibility to inform the site when these documents no longer need to be retained. According to 21 CFR 54.4(a), Investigator-related financial disclosure records must be retained for at least 2 years after the completion of the clinical trial or as specified in the Clinical Trial Agreement.

17.2.1. Investigator Responsibilities and Documentation

Before beginning the trial, the Principal Investigator will be asked to comply with ICH E6 and Title 21 of the CFR and any local regulatory requirements by assuring responsibility for and providing the following procedures and essential documents, including, but not limited to:

- Conducting trial according to current protocol approved by appropriate IRB/IEC.
- Personally conducting trial or personally supervising Sub-Investigators and other staff involved in trial conduct.
- Ensuring all trial staff are informed of their obligations to meet the Investigator commitments in Form FDA 1572 (US) or ICH E6 and other local regulations such as financial disclosure forms.

- Reading and understanding the current version of the rademikibart Investigator's Brochure (version 5 or above).
- Obtaining IRB/IEC review and approval for trial (per 21 CFR 56 [US] and ICH E6).
- Ensuring IRB/IEC provides initial and continuing review, and the approval of the trial complies with relevant local regulations (per 21 CFR 56 [US] and ICH E6); promptly informing IRB/IEC of changes in research activity or any unanticipated problems involving risk to participants.
- Making no changes to trial without approval by Sponsor and IRB/IEC review and approval (except when needed immediately to protect safety, rights, or welfare of trial participants).
- Notifying trial participants that rademikibart is investigational; obtaining informed consent from each participant per relevant regulations (per 21 CFR 50 [US] and ICH E6).
- Informing Sponsor or designee of unanticipated problems and AEs during trial (per 21 CFR 312.64 [US] and ICH E6); SAEs, serious AESIs and DILI to be reported within 24 hours and nonserious AESIs within 72 hours.
- Informing Sponsor or designee of UADEs during trial (per 21 CFR 812.150 [US]) within 24 hours.
- Maintaining adequate and accurate records (per 21 CFR 312.62 [US] and ICH E6); make records available for inspection (per 21 CFR 312.68 [US] and ICH E6).
- Complying with all other pertinent requirements of 21 CFR 312 (US) and ICH E6.
- An original Investigator-signed Investigator Agreement page of the protocol
- Providing an IRB/IEC-approved ICF, samples of site advertisements for recruitment, and any other written information regarding this trial that is to be provided to the participant or legal guardians.
- Form FDA 1572 (US) and/or form with equivalent information, fully executed, and all updates on a newly executed Form FDA 1572 (US) or equivalent.
- Curriculum vitae (CV) for the Principal Investigator and each Sub-Investigator will be listed on Form FDA 1572 (US) or ICH E6 or local equivalent. Current licensure must be noted on the CV. These will be signed and dated by the Principal Investigators and Sub-Investigators at trial start-up, indicating they are accurate and current.
- Providing financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54 (US) or relevant local equivalent.
- Providing laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with 42 CFR 493 (US) or relevant local equivalent.

17.2.2. Financial Disclosure

Investigators are required to inform the Sponsor of all disclosable financial interests or arrangements (including those of their spouse and dependent children), prior to trial initiation at the site, at trial completion, and 1 year after trial completion in accordance with 21 CFR Part 54. In addition, the Investigator or Sub-Investigators must promptly notify the Sponsor if there are any reportable changes that occur during the previously described period.

Disclosable financial interests or arrangements, or the absence thereof will be recorded on the Financial Disclosure for Clinical Investigators Form.

Any Investigator(s) added as investigational staff to the FDA 1572 form must complete the Financial Disclosure for Clinical Investigators Form at the start of his/her participation in the trial. The Financial Disclosure for Clinical Investigators Form for any Investigator(s) leaving the trial prior to completion will also be obtained.

18. PUBLICATION AND INFORMATION DISCLOSURE POLICY

All information provided by the Sponsor and all data and information generated by the site as part of the trial (other than a participant's medical records) are the sole property of the Sponsor.

For clinical interventional trials in patients, the Sponsor will post trial results on websites such as https://clinicaltrials.gov/ and https://eudract.ema.europa.eu/ in accordance with FDA and European Union reporting rules. Regardless of trial outcome, the Sponsor commits to submit for publication results of its interventional clinical studies according to the prespecified plans for data analysis. Wherever possible, the Sponsor also plans to submit for publication the results of any nonclinical or technology studies while protecting any proprietary information.

Any publication or presentation of the results of this trial may only be made in compliance with the provisions outlined in the executed Clinical Trial Agreement. The Sponsor has developed a policy for the publication of scientific and clinical data that follows the recommendations of the International Committee of Medical Journal Editors (ICMJE), the CONSORT group and Good Publication Practice (GPP).

When the trial is completed or prematurely terminated, the Sponsor or designee will ensure a CSR is written in compliance with ICH E3 (Structure and Content of Clinical Study Reports) and submitted to the regulatory authorities, as required by the applicable regulatory requirement(s). Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the CSR. The Investigator will be provided reasonable access to statistical tables, listings, and figures, as well as relevant reports, and will have the opportunity to review the complete trial results.

18.1. Confidentiality

All information provided by the Sponsor. and all data and information generated by the site as part of the trial (other than a participant's medical records) will be kept confidential by the Investigator and site staff. This information and data will not be used by the Investigator or other site personnel for any purpose other than conducting the trial and will not be released to any unauthorized third party without prior written approval of the Sponsor. These restrictions do not apply to the following: 1) information that becomes publicly available through no fault of the Investigator or site staff, 2) information that must be disclosed in confidence to an IRB/IEC solely for the evaluation of the trial results, 3) information that must be disclosed in order to provide appropriate medical care to a trial participant, or 4) trial results that may be published as described in the Publication and Information Disclosure Policy section. If a written contract for the conduct of the trial is executed and that contract includes confidentiality provisions inconsistent with this statement; that contract's confidentiality provisions shall apply rather than this statement, provided, however, that the confidentiality provisions in any written contract shall not be less restrictive than this statement.

The Investigator agrees to comply with all applicable national, state, and local laws and regulations relating to the privacy of participants' health information. The Investigator shall ensure that trial participants authorize the use and disclosure of protected health information in accordance with the privacy regulations of the HIPAA and in a form satisfactory to the Sponsor.

The participant's contact information will be securely stored at each clinical site for internal use during the trial. Throughout the trial, a participant's source data will only be linked to the

Sponsor's clinical trial database or documentation via a unique ID number. Copies of any participant source documents that are provided to the Sponsor must have certain personally identifiable information removed (ie, participant name, address, and other identifier fields not collected in the participant's eCRF). At the end of the trial, all records will continue to be kept in a secure location for as long a period as dictated by the IRB/IEC and institutional regulations.

To comply with ICH guidelines for GCP and to verify compliance with this protocol, the Sponsor requires that the Investigator permit its monitor or designee's monitor, representatives from any regulatory authority, the Sponsor's designated auditors, and the appropriate IRBs/IECs to review the participant's original medical records (source data or documents), including, but not limited to, clinical laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a participant's trial participation, and autopsy reports. Access to a participant's original medical records requires the specific authorization by the participant as part of the informed consent process.

19. APPENDICES

APPENDIX A. SCHEDULE OF ASSESSMENTS

The SoA for participants who complete the planned treatment is presented in Table 5.

Table 5: Schedule of Assessments

Procedures	Screening		Randomization/ Baseline/ Administration	IP Treatment Assessment						Follow-up
VISIT	**V1a**[a]	**V1b**[a,b]	**V2**[c]	**V3**[d]	**V4**[d]	**V5**	**V6**	**V7**[e]	**V8**	**V9**
DAY	**Up to 26 weeks to D-1**	**Up to 48 hours to D0**	**0**	**1**	**2**	**3**	**7 ±2 days**	**14 ±2 days**	**28 ±3 days**	**56 ±3 days (EOT)**
WEEK							**1**	**2**	**4**	**8**
Written informed consent and HIPAA	X	X[a]								
Demographics	X	X[a]								
Previous medical and surgical history[f]	X	X[a]								
Chest X-ray or CT		X								
Verify eligibility criteria	X	X								
Smoking status review	X	X					X		X	X
Prior & concomitant medications	X	X	X	X	X	X	X	X	X	X
e-diary registration & training[g]		X								
Review e-diary			X			X	X		X	X
Interventional Treatment /Rescue Medication										
Randomization and assignment of trial product kit number			X							
IP administration			X							
Review rescue medication use			X	X	X	X	X		X	X

Procedures	Screening		Randomization/ Baseline/ Administration	IP Treatment Assessment						Follow-up
VISIT	**V1a**[a]	**V1b**[a,b]	**V2**[c]	**V3**[d]	**V4**[d]	**V5**	**V6**	**V7**[e]	**V8**	**V9**
DAY	**Up to 26 weeks to D-1**	**Up to 48 hours to D0**	**0**	**1**	**2**	**3**	**7 ±2 days**	**14 ±2 days**	**28 ±3 days**	**56 ±3 days (EOT)**
WEEK							**1**	**2**	**4**	**8**
Safety										
Complete physical examination[h]	X	X	X							X
Symptom-directed physical examination[h]				X	X	X	X		X	
Assess injection site(s) [i]			X	X	X	X	X		X	
Body weight, height[j]	X	X	X						X	X
Vital signs, oxygen saturation[k]	X	X	X	X	X	X	X		X	X
ECG (12 lead)[l]	X	X	X				X			X
Hematology, clinical chemistry, urinalysis[m]	X	X[n]	X[n]				X		X	X
Pregnancy (β-hCG blood) test[o]	X	X								
Urine pregnancy test			X[p]						X	X
AE reporting, including SAEs and AESIs	X	X	X	X	X	X	X	X	X	X

Procedures	**Screening**		**Randomization/ Baseline/ Administration**	**IP Treatment Assessment**						**Follow-up**
VISIT	**V1a**[a]	**V1b**[a,b]	**V2**[c]	**V3**[d]	**V4**[d]	**V5**	**V6**	**V7**[e]	**V8**	**V9**
DAY	**Up to 26 weeks to D-1**	**Up to 48 hours to D0**	**0**	**1**	**2**	**3**	**7 ±2 days**	**14 ±2 days**	**28 ±3 days**	**56 ±3 days (EOT)**
WEEK							**1**	**2**	**4**	**8**
Pharmacokinetics/Immunogenicity/Pharmacodynamic										
Plasma PK samples for rademikibart concentration[q]			X			X	X		X	X
Blood sample for biomarker analysis			X				X		X	X
FeNO	X	X	X			X	X		X	X
ADAs and nAbs[q]			X						X	X
Efficacy										
Assessment (by Investigator) of COPD exacerbation			X	X	X	X	X	X	X	X
Venous blood gas analysis[r]			X	X	X	X				
Spirometry (pre-BD)[s]	X						X		X	X
Spirometry (post-BD)[t]	X	X	X	X[u]	X[u]	X	X		X	X
EXACT-PRO[v]			Daily (e-diary) from V2 to Week 8							
Dyspnea NRS		Daily (e-diary) from Screening V1b to Week 8								
CAT[w]			X				X	X	X	X
SGRQ[x]			X						X	X
Health care resource utilization			X				X		X	X
Time to Ready-for-Discharge			←				→			

ADA = anti-drug antibodies; AE = adverse event; AESI = adverse event of special interest; β-hCG = human chorionic gonadotropin-beta; BD = bronchodilator; CAT= COPD Assessment Test; COPD = chronic obstructive pulmonary disease; CT = computed tomography; D = day; ECG = electrocardiogram; ED = emergency department; e-diary = electronic diary; EOT = End of Trial; EXACT PRO = Exacerbations of COPD Tool – Patient-Reported Outcome; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; HIPAA = Health Insurance Portability and Accountability Act; ID = identification; IP = investigational product; LABA = long-acting β2-adrenergic agonists; LAMA = long-acting muscarinic antagonist; MDI = metered dose inhaler; nAb = neutralizing antibody; NRS = Numerical Rating Scale; PARC = pulmonary and activation-regulated chemokine; PK = pharmacokinetic(s); PRN = pro re nata; SABA = short-acting β-agonists; SAE = serious adverse event; SGRQ = St. George's Respiratory Questionnaire; V = visit

Note: Participants will be monitored at the trial site for a minimum of 2 hours after IP administration.

a According to the timepoint at which participants consent to the trial, the Screening procedure will be as follows:

- For participants who consent to participate in the trial while in a stable condition, they should complete V1a after providing written informed consent and eligibility has been verified. Investigators or their designees will contact the participants by telephone approximately every 4 weeks after V1a to collect any changes in concomitant medications and any SAEs. If a participant's symptoms worsen, such as increased breathlessness, cough, wheeze, chest tightness, sputum production, or sputum discoloration, this may indicate that the participant is experiencing an exacerbation. Participants should be reminded to contact the site to report worsening symptoms at the onset of the exacerbation, before taking any medication. They should then visit the ED or urgent healthcare clinic associated with the trial center to complete V1b (exacerbation visit) and further verify eligibility criteria. Written informed consent, HIPAA authorization, participant demographics, and previous medical and surgical history will not be collected again at V1b. However, medical conditions that started after V1a should be collected.
- For participants who consent to participate in the trial during the urgent healthcare visit for an acute COPD exacerbation, V1b should be completed immediately after providing written informed consent and verifying eligibility.

b The Screening Period after Screening V1b is up to 48 hours. Any procedures completed as part of the assessment and treatment of the COPD exacerbation may be used for Screening (eg, hematology, clinical chemistry, urinalysis, ß-hCG if applicable, spirometry, chest X-ray or CT, ECG). Note that the maximum combined number of chest X-rays and/or CT scans must not exceed 2 for screening.

c Randomization/Baseline Visit is defined as Day 0 (V2). Screening V1b and Day 0 (V2) may be the same day or up to 48 hours apart. All assessments at Visit 2 (Day 0) are to be conducted pre-IP dose administration with the exception of the assessment of SC injection sites and post-IP administration vital sign measurements.

d V3 and V4 are for participants who are hospitalized for current acute COPD exacerbation. Hospitalized participants discharged from the hospital prior to V3 or V4, or participants that were not hospitalized, have the option to consent to return to the trial site or have a home health care visit for spirometry assessments at Visit 3 and Visit 4.

e At V7, participants will be contacted by telephone.

f Medical history includes COPD history, COPD exacerbation history, past and current medical conditions (including cardiovascular and cerebrovascular medical history, surgical history), and substance usage.

g Participants will be trained on home use of the e-diary at Visit 1b and throughout the trial on an as needed basis. Participants will complete the assessment of EXACT-PRO every evening, and Dyspnea NRS and usage of short-acting rescue medications via e-diary twice daily at home.

h A complete physical examination will cover general appearance, dermatological, head, ears, eyes, nose, throat, respiratory, cardiovascular,

abdominal, neurological, musculoskeletal, and lymphatic body systems. A complete physical examination will be conducted during Screening Visits 1a and 1b, at Baseline, and at the EOT visit. At all other visits, a symptom-directed physical examination may be conducted at the discretion of the Investigator.

i Participants will be monitored for a minimum of 2 hours after IP administration. Injection sites will be assessed at 30 minutes (±10 minutes) post-injection and then at 2 hours (±30 minutes) post-injection.

j Height will only be measured at V1a or V1b. The participant's height must be measured without shoes and weight must be determined in indoor clothing and without shoes.

k Vital signs, including body temperature, respiratory rate (breath per minute), pulse (beats per minute), and BP (mmHg), will be measured in the seated position following at least 5 minutes rest. BP and pulse measurements will be assessed with a completely automated device whenever possible. Manual techniques will be used only if an automated device is not available. Vital signs will be measured prior to the spirometry maneuvers. Oxygen saturation will be measured by using pulse oximeter. Participants will be monitored for a minimum of 2 hours after IP administration. Vital sign measurements will be performed at 30 minutes (±10 minutes) post-injection and then at 1 hours (±10 minutes) and 2 hours (±15 minutes) post injection.

l 12-lead ECG measurements are collected and assessed at local sites. Measurements will be performed with the participant resting in a supine position for approximately 5 minutes before each reading and should be carried out after measurement of vital signs and before spirometry. ECGs should be performed before blood is drawn during visits requiring blood draws.

m Hematology, clinical chemistry, and urinalysis parameters are provided in Appendix C.

n Screening V1b: Due to the short screening window, local laboratory results will be used for the purpose of determining the participant's eligibility for randomization. Local laboratory samples should be taken at Screening V1b and the results should be received and reviewed prior to randomization to allow review of the applicable eligibility criteria. If local laboratory results from the assessment of the current COPD exacerbation are already available within 72 hours prior to Screening V1b, these results can be used for determination of participant's eligibility. For all randomized participants, a sample for central laboratory analysis should be obtained before IP administration on Day 0 as baseline.

o For women of childbearing potential, must be negative prior to IP administration. Analyzed at a local laboratory.

p For women of childbearing potential only if Screening and the Baseline Visit (Day 0) are not on the same day. Analyzed at a local laboratory.

q On Day 0, PK and ADA/nAb samples will be collected prior to administration of IP. On days when PK and ADA/nAb sample collection are coinciding, the samples can be taken at the same time.

r Venous blood gas will only be assessed in hospitalized participants.

s Spirometry assessments include FEV_1, and FVC (both the absolute measurement, and the percentage of predicted normal value will be recorded. Spirometry will be performed preferably in the morning; afternoon is allowable in the exceptional circumstance when morning spirometry cannot be performed. If the participant can tolerate BD washout, at Visit 6, Visit 8, Visit 9, and on the day of discharge (only for hospitalized participants), pre-BD spirometry will be performed prior to administering maintenance COPD medication(s). Participants should withhold their usual maintenance therapies on the day(s) when pre-BD spirometry is being performed as below: Withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours; withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours); withholding the last dose of ipratropium bromide for at least 8 hours; withholding the last dose of LAMA for at least 24 hours. This washout period will be verified before performing the measurements.

t If the participant's condition allows, post-BD FEV_1 will be conducted approximately 15 to 30 minutes after the participant administers 4 inhalations of albuterol (salbutamol) via MDI (ie, total of 400 mcg) using a spacer device. It is anticipated that participants who are randomized into the trial will receive albuterol as part of the routine treatment of COPD exacerbation during V2. In this case, spirometry should be scheduled to coincide with this treatment to allow post-BD recordings to be measured.

u For hospitalized participants, post-BD spirometry should also be performed at Visit 3 and Visit 4 provided the participant's condition allows. Hospitalized participants discharged from the hospital prior to Visit 3 and Visit 4, or participants that were not hospitalized for the index COPD exacerbation, they have the option to consent/assent to return to the trial site or have a home health care visit for spirometry assessments at Visit 3 and Visit 4.

v Participants should complete the EXACT-PRO as follows: At V2, complete the assessment while at the site as the first assessment before IP administration and prior to completing other trial assessments/procedures (may be completed in the morning or the afternoon); thereafter, it will be completed daily in the evening (typically at bedtime).

w Participants should complete CAT prior to the SGRQ and other trial assessments/procedures. CAT will be captured electronically using a handheld device at the site visit or paper questionnaires at the telephone call visit (V7). Electronic upload of a participant completed paper questionnaire is permitted when use of the electronic questionnaire is not possible.

x SGRQ will be captured electronically using a handheld device at the site. Participants should complete the SGRQ after the CAT and prior to other trial assessments/ procedures.

APPENDIX B. CONTRACEPTION AND PREGNANCY TESTING

Definition Related to Childbearing Potential

Women of Childbearing Potential (WOCBP) must use highly effective birth control throughout the trial including the Follow-up Period.
Women in the following categories are considered WOCBP (fertile):

1. Following menarche
    - From the time of menarche until becoming postmenopausal unless permanently sterile (see below)
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
        - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrollment.
    - Permanent sterilization methods (for the purpose of this trial) include:
        - Documented hysterectomy
        - Documented bilateral salpingectomy
        - Documented bilateral oophorectomy
        - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining trial entry.

NOTE: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of IP, additional evaluation should be considered.

CONTRACEPTIVES[a] ALLOWED DURING THE TRIAL INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – Oral – Intravaginal – Transdermal – Injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] – Oral – Injectable
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the participant.)
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. [b] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c] Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
[d] Considered effective, but not highly effective - failure rate of ≥1% per year.
NOTE: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

APPENDIX C. CLINICAL SAFETY LABORATORY ASSESSMENTS

Laboratory Tests	Parameters	
Hematology	• Platelet count	
	• Red blood cell (RBC) count	
	• White blood cell (WBC) count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils	
	• Hemoglobin	
	• Hematocrit	
Clinical Chemistry	• Blood urea nitrogen (BUN) • Potassium • Creatinine • Sodium • Calcium • Glucose • Chloride • Bicarbonate • Uric acid • Albumin • C-reactive protein[a] • Creatinine Phosphokinase (CPK) • Triglycerides	• Aspartate aminotransferase (AST) • Alanine aminotransferase (ALT) • Alkaline phosphatase (ALP) • Gamma-glutamyltransferase (GGT) • Lactate dehydrogenase (LDH) • Total and direct bilirubin • Total protein • Total cholesterol
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase • Microscopic examination (if blood or protein is abnormal)	
Pregnancy Testing	• Highly sensitive human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential) (serum at screening only, urine at subsequent visits),	

[a] C-reactive protein is a pharmacodynamic marker.

APPENDIX D. INJECTION SITE REACTION ASSESSMENT TOOL

The Injection Site Assessment Tool provided in Table 6 is provided as an aid in the assessment of common symptoms of injection site reaction. The Investigator may use their own judgement and description of symptoms in the assessment of injection sites following administration of IP. An Injection Site Reaction should be reported as an AE if the Investigator judges the reaction as clinically significant. A parameter grade of less than 2 is generally considered not clinically significant but the Investigator should use their judgement in the reporting of AEs. See Section 11.2.5.

Table 6: Injection Site Reaction Assessment

Parameter	Grade	Description
Erythema	0	None
	1	Very slight (barely perceptible)
	2	Slight (well defined)
	3	Moderate
	4	Severe (beet redness) to slight eschar formation (injuries in depth)
Drainage	0	None
	1	Serous
	2	Serosanguinous
	3	Bloody
	4	Purulent
Edema	0	None
	1	Very slight (barely perceptible)
	2	Slight (edges well defined)
	3	Moderate (raised approximately 1 mm)
	4	Severe (raised >1 mm and beyond areas of exposure)
Induration	0	None
	1	Minimal
	2	Mild (spongy tissue)
	3	Moderate (firm, warm)
	4	Severe (hard, red, hot, crepitus)
Hematoma	0	None
	1	Minimal
	2	Mild
	3	Moderate
	4	Severe

APPENDIX E. DYSPNEA NUMERICAL RATING SCALE

On a scale from 0 to 10

Indicate how much shortness of breath you are having right now

With **0 = no shortness of breath**

And **10 = shortness of breath as bad as can be**

Circle the number:

0 1 2 3 4 5 6 7 8 9 10

Numeric rating scale assessing dyspnea

Adapted from (Gift and Narsavage 1998)

APPENDIX F. SGRQ

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE ORIGINAL ENGLISH VERSION

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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UK/ English (original) version 1

continued…

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St. George's Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have had over the past 4 weeks.

Please tick (✓) *one box for each question*:

	most days a week	several days a week	a few days a month	only with chest infections	not at all
1. Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 4 weeks, I have had attacks of wheezing:	☐	☐	☐	☐	☐

5. During the past 4 weeks, how many severe or very unpleasant attacks of chest trouble have you had?

Please tick (✓) *one*:

- more than 3 attacks ☐
- 3 attacks ☐
- 2 attacks ☐
- 1 attack ☐
- no attacks ☐

6. How long did the worst attack of chest trouble last?
(Go to question 7 if you had no severe attacks)

Please tick (✓) *one*:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in an average week, how many good days (with little chest trouble) have you had?

Please tick (✓) *one*:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day is good ☐
- every day is good ☐

8. If you have a wheeze, is it worse in the morning?

Please tick (✓) *one:*

- No ☐
- Yes ☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your chest condition?

Please tick (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problem ☐

If you have ever had paid employment.

Please tick (✓) *one*:

- My chest trouble made me stop work altogether ☐
- My chest trouble interferes with my work or made me change my work ☐
- My chest trouble does not affect my work ☐

Section 2

Questions about what activities usually make you feel breathless <u>these days</u>.

Please tick (✓) in ***each box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Getting washed or dressed	☐	☐
Walking around the home	☐	☐
Walking outside on the level	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or games	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 3

Some more questions about your cough and breathlessness <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough hurts	☐	☐
My cough makes me tired	☐	☐
I am breathless when I talk	☐	☐
I am breathless when I bend over	☐	☐
My cough or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

Questions about other effects that your chest trouble may have on you <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot get my breath	☐	☐
I feel that I am not in control of my chest problem	☐	☐
I do not expect my chest to get any better	☐	☐
I have become frail or an invalid because of my chest	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My medication does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My medication interferes with my life a lot	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your breathing.

	Please tick (✓) in ***each box*** that applies to you ***because of your breathing***: True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time	☐	☐
I walk slower than other people, or I stop for rests	☐	☐
Jobs such as housework take a long time, or I have to stop for rests	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 7

We would like to know how your chest <u>usually</u> affects your daily life.

	Please tick (✓) in ***each box*** that applies to you ***because of your chest trouble***: True	False
I cannot play sports or games	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do housework	☐	☐
I cannot move far from my bed or chair	☐	☐

continued…

St. George's Respiratory Questionnaire

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or walking the dog

Doing things at home or in the garden

Sexual intercourse

Going out to church, pub, club or place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

. . . . . .

. . . . . .

. . . . . .

. . . . . .

Now would you tick in the box (one only) which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do ☐

It stops me doing one or two things I would like to do ☐

It stops me doing most of the things I would like to do ☐

It stops me doing everything I would like to do ☐

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.

UK/ English (original) version 6

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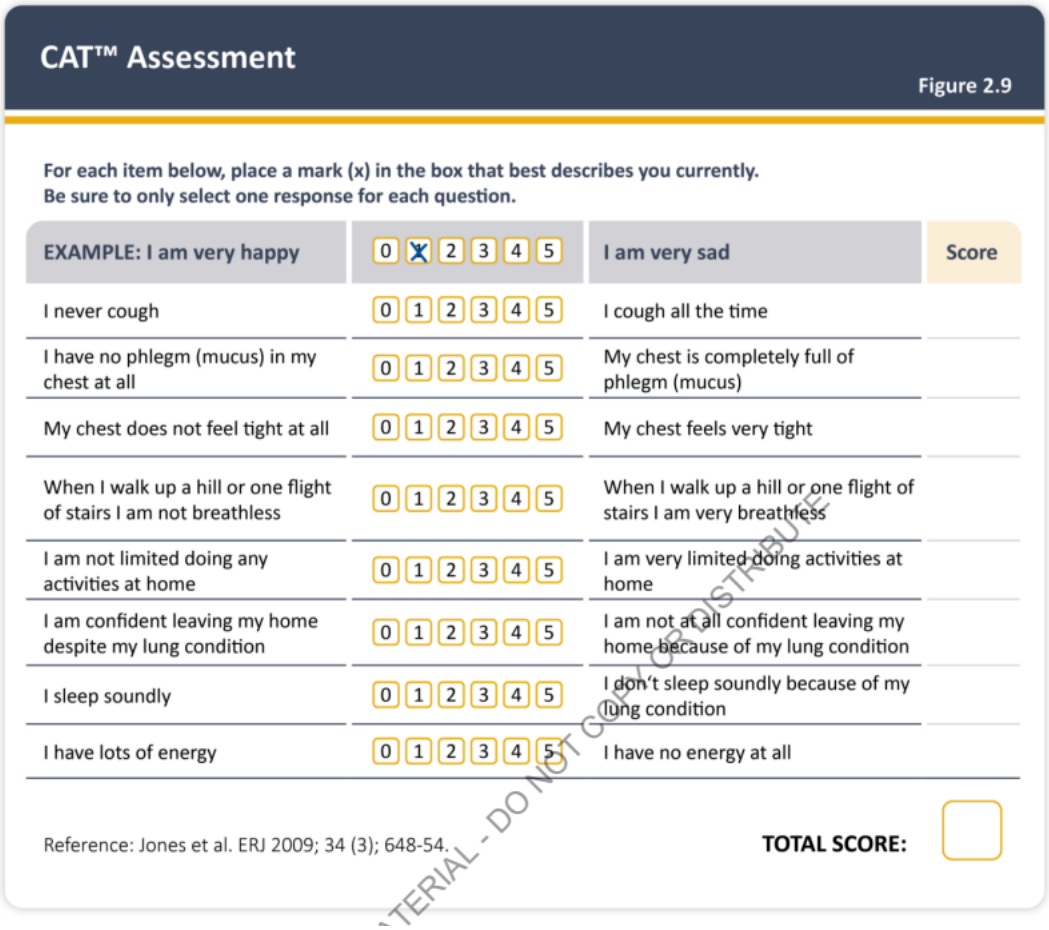
APPENDIX G. CAT



CAT™ Assessment

Figure 2.9

For each item below, place a mark (x) in the box that best describes you currently.
Be sure to only select one response for each question.

EXAMPLE: I am very happy	0 X 2 3 4 5	I am very sad	Score
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	

Reference: Jones et al. ERJ 2009; 34 (3); 648-54.

TOTAL SCORE:

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APPENDIX H. EXACT-PRO

The EXACT-PRO as formatted for personal digital assistant (pda)

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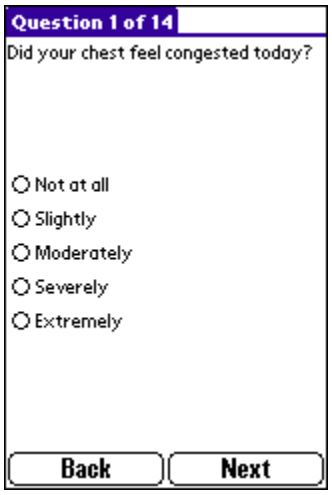

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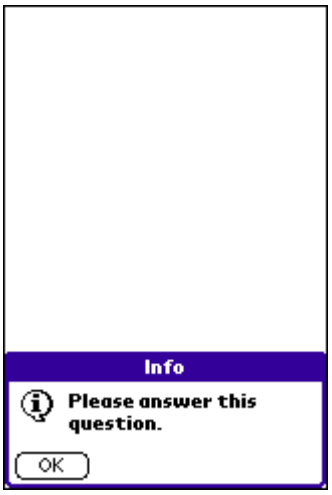

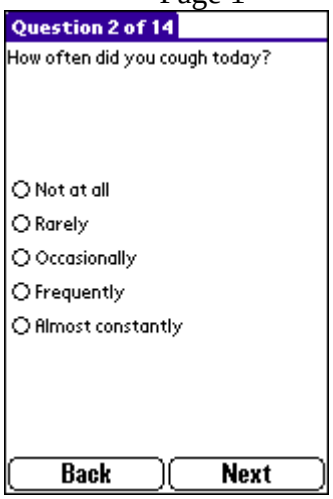

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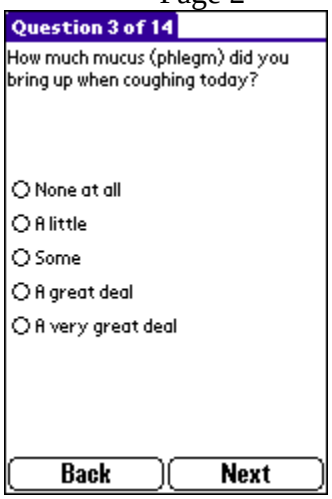

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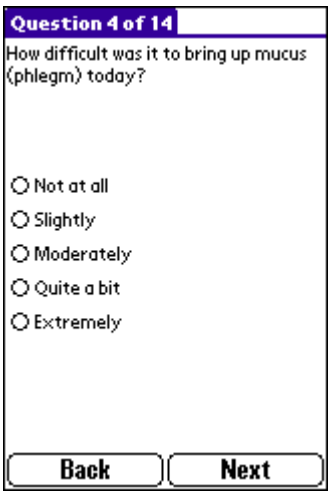

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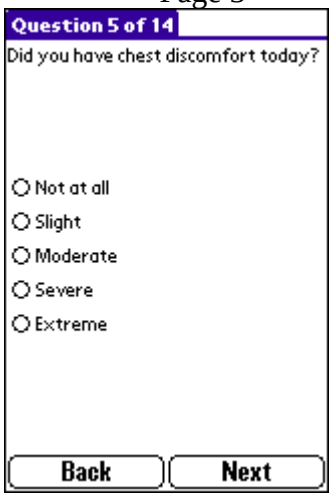

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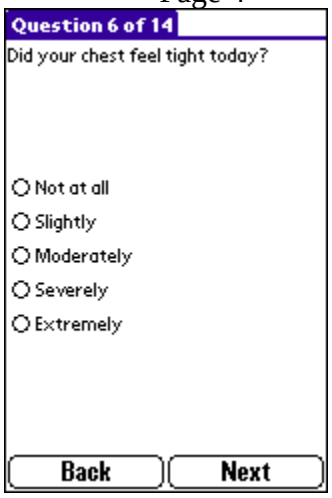

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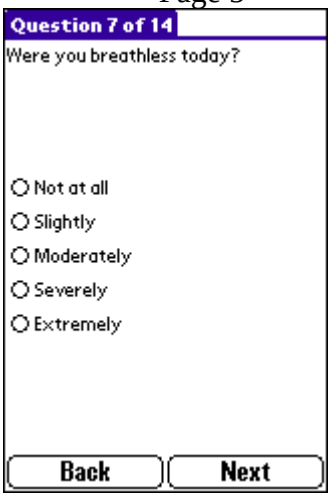

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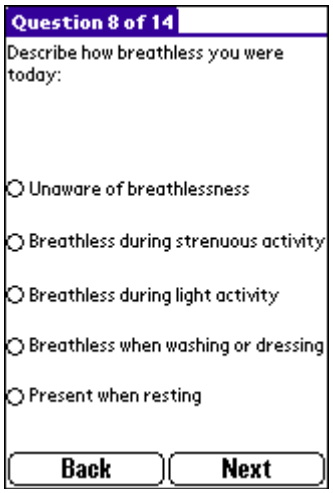

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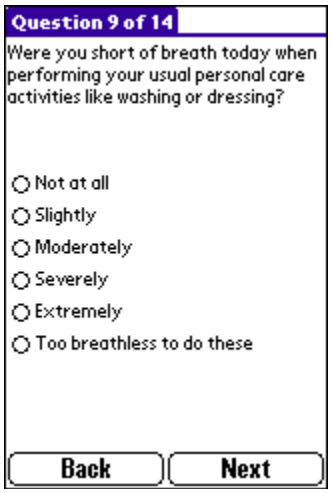

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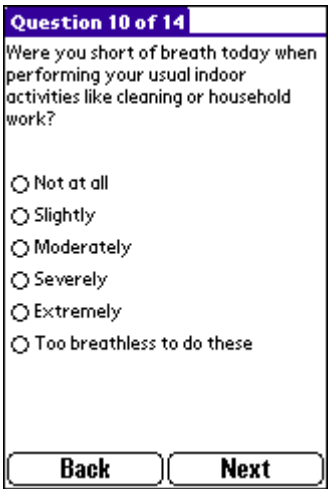

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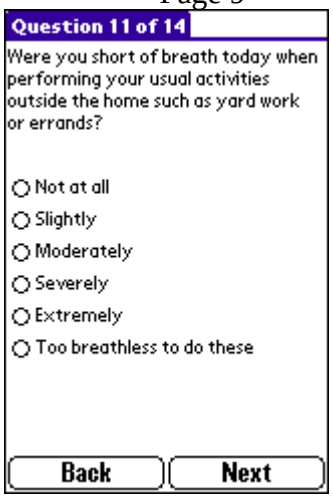

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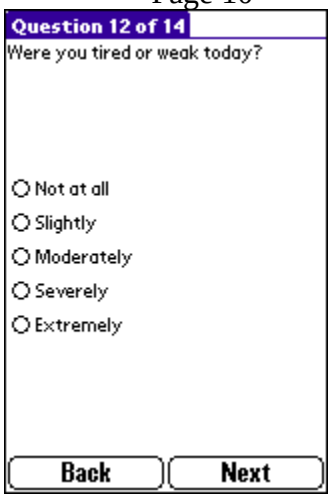

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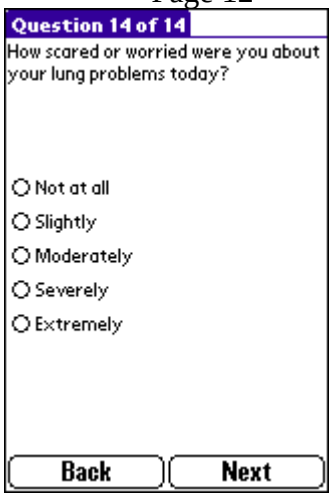

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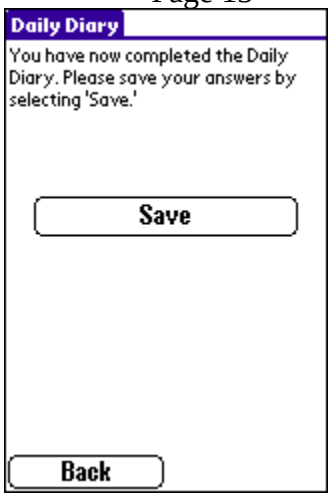

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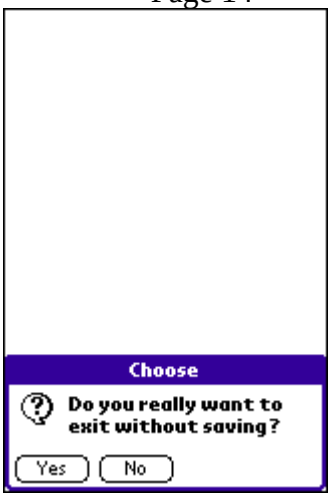

APPENDIX I. LIST OF PROHIBITED LIVE ATTENUATED VACCINES

The following list of prohibited live attenuated vaccines is indicative and is not exhaustive:

- Bacillus Calmette-Guérin antituberculosis vaccine.
- Chickenpox (Varicella).
- Intranasal influenza (FluMist-Influenza); inactive influenza vaccine delivered by injection is permitted.
- Measles (Rubeola).
- Measles-mumps-rubella combination.
- Measles-mumps-rubella-varicella combination.
- Mumps.
- Oral polio (Sabin).
- Oral typhoid.
- Rotavirus.
- Rubella.
- Smallpox (Vaccinia).
- Zostavax (for shingles; note that Shingrix is *not* live).
- Yellow fever.
- Japanese Encephalitis Vaccine (only some formulations, eg, Imojev).

APPENDIX J. ADDITIONAL SAFETY REPORTING DEFINITIONS FOR ADVERSE EVENTS OF SPECIAL INTEREST

Table 7: List of Opportunistic Infections

The following is a list of infections that are indicative of opportunistic infections, but the list is not exhaustive. Refer to Winthrop et al. 2015 for additional information (Winthrop KL et al. 2015).	
• Aspergillosis • Blastomycosis dermatitidis (endemic in the south-eastern and south-central states US, along Mississippi and Ohio Rivers) • Candidiasis (only systemic or extensive mucosal or cutaneous candidiasis) • Coccidioides immitis (endemic south-western US and Central and South America) • Cryptococcus • Cytomegalovirus • Herpes simplex (disseminated)	• Herpes zoster (disseminated; ophthalmic; involvement of 2 or more dermatomes) • Histoplasmosis (pulmonary or disseminated; most common tropical areas Tennessee-Ohio-Mississippi river basins) • Listeriosis • Mycobacterium tuberculosis • Mycobacterium avium • Nontuberculous mycobacterium • Pneumocystis pneumonia (PCP)

Table 8: Definition of Anaphylaxis

Should any one of the following 3 criteria be met, the anaphylaxis is likely to occur:
1. Acute onset (minutes to several hours) of certain illness with involvement of the skin or mucosal tissue, or both (eg, generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula) and associated with at least one of the following: a. Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, PEF decreased, hypoxemia) b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur after exposure to a likely allergen for that patient (minutes to several hours): a. Involvement of the skin-mucosal tissue (eg, generalized urticaria, pruritus - flushing, swollen lips-tongue-uvula) b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, PEF decreased, hypoxemia) c. Reduced BP or associated symptoms (e.g., hypotonia (collapse), syncope, incontinence) d. Persistent gastrointestinal symptoms (e.g., abdominal colic, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours); systolic blood pressure (SBP) lower than 90 mmHg or reduction from baseline greater than 30%.
Source: (Sampson et al. 2006)

APPENDIX K. DRUG-INDUCED LIVER INJURY

Drug-induced liver injury (DILI) refers to a liver injury induced by various chemical drugs, biological products, herbal medicines and their metabolites or even excipients.

1. Criteria for fulfillment of Hy's Law

Hy's Law can facilitate assessment of severe liver injury predominated by hepatocellular injury. It specifically refers to cases that meet all of the following 3 criteria:

For participants with normal liver function tests at baseline:

1. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3× upper limit of normal (ULN) during treatment period;
2. Total bilirubin > 2× ULN during treatment period; without cholestasis at baseline (serum alkaline phosphatase [ALP] increased);
3. No other identifiable causes explaining the simultaneous elevation of aminotransferases and total bilirubin, such as viral hepatitis A, B, C or E or other acute liver diseases, or concomitant use of other drugs that may induce liver injury.

2. Retest and confirmation

For participants with normal liver biochemistry parameters at baseline, if ALT or AST > 3× ULN is detected, the liver-related biochemistry parameters should be retested within 48 to 72 hours whenever possible to confirm and access the trend of changes. When ALT or AST is significantly elevated above 3× ULN (e.g., ALT or AST increased to > 5× ULN) or total bilirubin is significantly elevated above 2× ULN, immediate retest of the liver biochemistry parameters is recommended.

For participants with abnormal liver biochemistry parameters at baseline, a comprehensive evaluation should be made taking into account the above criteria, with reference to the following criteria as recommended:

1. ALT or AST ≥ 3× baseline value during treatment period;
2. An increase in total bilirubin by 1× ULN during treatment period; without cholestasis at baseline (serum ALP increased);
3. No other identifiable causes explaining the simultaneous elevation of aminotransferases and total bilirubin, such as viral hepatitis A, B, C or E or other acute liver diseases, or concomitant use of other drugs that may induce liver injury.

In addition to repeated testing of AST and ALT, liver biochemistry parameters should also include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyltransferase, prothrombin time/international normalized ratio, and alkaline phosphatase. A detailed medical history and relevant information collection are recommended, including history of alcohol use, acetaminophen, recreational drugs, various supplements, family medical history, travel history, history of contact with patients with jaundice, history of surgery, blood transfusion, liver disease or allergic diseases, history of possible occupational chemical exposure, etc. Further examinations can also include the detection of hepatitis A, B, C, D and E as well as imaging of the hepatobiliary system (such as CT, ultrasound).

All cases confirmed by repeat testing to meet the above laboratory criteria for AST/ALT and total bilirubin increased should be considered as a suspected DILI (Hy's Law) case if no other causes of liver function test abnormalities have been identified. These suspected DILI (Hy's Law) cases should be reported to the Sponsor within 24 hours.

A suspected DILI (Hy's Law) case will become a confirmed case only after all the results of the reasonable tests have been available and other etiologies have been excluded.

3. Close observation

Participants with confirmed liver injury should be closely monitored, including collecting a more detailed medical history and dynamically observing changes in the liver biochemistry parameters and coagulation function. Based on the participant’s condition, liver biochemical parameters and coagulation function should be retested. Initially, liver function tests should be repeated 2 to 3 times per week. If the abnormalities stabilize or the investigational product has been discontinued and the participant is asymptomatic, the frequency of repeat testing can be reduced to once per week.

4. Follow up

Cases with liver injury should be followed up until all abnormal parameters have recovered and stabilized at the normal or baseline level, or a relevant clinical outcome event (eg, chronic liver injury, cirrhosis, liver failure, liver transplant, death) has occurred. It should be noted that liver injury may continue evolving even after discontinuation of the related drug.

APPENDIX L. PROTOCOL VERSION HISTORY

Protocol Version	Date	Type of Amendment	Region(s) Impacted
1.0	20 Feb 2025	N/A	N/A
1.1	20 Mar 2025	Nonsubstantial	Global
1.2	09 Jun 2025	Nonsubstantial	Global

N/A = not applicable

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